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Vanderbilt, Beckman,Duke,Stanford,Wellman

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Vanderbilt University FEL Center
410 24th Avenue South - Nashville, TN 37235

8. PERFORMING ORGANIZATION REPORT NUMBER
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VANDERBILT UNIVERSITY
NASHVILLE, TENNESSEE 37235 TELEPHONE (615) 322-7311

W.M. Keck Foundation Free-Electron Laser Center • Direct phone 343-6146

7 October 1998

Dr. Michael T. Marron
Naval Research Laboratory
Code 6900
4555 Overlook Avenue, SW
Washington, D.C. 20357-5348

Re: Grant N00014-96-1-0810

Dear Mike:

This constitutes the final report for the contract entitled "Vanderbilt University FEL Users Conference." All of the funds have been expended for the fall 1996 MFEL Contractors Meeting (the symposium) and for FEL related travel as approved by the ONR. Enclosed are four copies of the symposium proceedings as called for by the terms of the award.

Please let me know if you need any additional information.

Sincerely,

Glenn Edwards, Director
W.M. Keck FEL Center

Enclosures

cc: ONR Atlanta
Defense Technology Information Center

MFEL CONTRACTORS MEETING
PARTICIPANTS
Vanderbilt University FEL Center
November 1 & 2, 1996

Beckman
Berns, Michael
Milner, Thomas
Peavy, George
Tromberg, Bruce

Duke
Chen, Longen
Nashold, Blaine
Rose, John
Sheetz, Michael
Straub, David

Naval Research Lab
Ting, Antonio

ONR
Alberte, Randall
Case, David
Marron, Michael
Rupnik, John
Schlossberg, Howard

Stanford
Benaron, David
Erramilli, Shyamsunder
Schwettman, Alan
Smith, Todd

Wellman
Anderson, R. Rox
Deutsch, Thomas
Doukous, Apostolos
Flotte, Thomas
Hasan, Tayyaba
Lin, Charles
Nishioka, Norm
Parrish, John
Schomacker, Kevin

Accommodations
The Vanderbilt Holiday Inn, 2613 West End Avenue, Nashville, TN 37203
(615) 327-4707

Transportation
The hotel is approximately 20 minutes from the airport and about 8 blocks from the FEL Center. Grey Line Shuttle Service runs every 30 minutes from the airport to the Holiday Inn and, of course, cabs are also available. If you rent a car please remember you can not park on campus. The Holiday Inn is within walking distance of the FEL, providing the weather cooperates.

Meeting Location
The meeting will be held in the Heritage Room of the University Club (next door to the FEL Center) at Kirkland Avenue and 24th Avenue South. There will be campus maps available at the hotel front desk when you check-in.

A continental breakfast will be available at 7:30AM Friday. The meeting begins at 8:00AM.

* PLEASE CALL VALORIE @ **615-343-6146** IF YOU HAVE ANY QUESTIONS *

MFEL CONTRACTORS MEETING - PARTICIPANTS

Beckman (4)
Berns, Michael
Milner, Thomas
Peavy, George
Tromberg, Bruce

Duke (6)
Chen, Longen
Nashold, Blaine
Rose, John
Sheetz, Michael
Straub, David

Naval Research Lab (1)
Ting, Antonio

ONR (6)
Alberte, Randall
Case, David
Marron, Michael
Roberson, Charles
Rupnik, John
Schlossberg, Howard

Stanford (4)
Benaron, David
Erramilli, Shyamsunder
Schwettman, Alan
Smith, Todd

Wellman (9)
Anderson, R. Rox
Deutsch, Thomas
Doukous, Apostolos
Flotte, Thomas
Hasan, Tayyaba
Lin, Charles ~~Delta~~ flight cancelled
Nishioka, Norm
Parrish, John
Schomacker, Kevin ~~Delta~~ flight cancelled

Vanderbilt (19)
Brau, C.A.
Carroll, F.
Casagrande, V.
Copeland, M.
Davidson, J.
Edwards, G.
Gabella, B.
Garrett, G.
Gilligan, J.
Joos, Karen
McIntyre, O.
Keay, Brian
McKanna, J.
Park, Hee
Reinisch, L.
Shen, Jin
Tolk, N.
Traeger, B.
Williams, R.

Laser-Assisted Cartilage Reshaping for Reconstructive Surgery

UCI - Beckman Laser Institute and Medical Clinic

Animal Models: Selected ex-Vivo cartilage harvested from porcine, rabbit, and chicken animals

Clinical Applications: Surgical correction of auricular and nasal deformities, reconstruction of tracheal and laryngeal defects

Equipment/Task	**1997**				**1998**			
	1	2	3	4	1	2	3	4
Penetration Depth/Wavelength (Infrared Detection System)	x	x	x	x				
Catalytic Techniques (Spray Cooling, Electric Field, Geometry)	x	x	x	x	x	x		
Optimal Dose-Exposure Times (Beam scanning system, strength measurement)	x	x	x	x	x	x		
Feedback System (Optical and/or Thermal)			x	x	x	x	x	x

Laser-Assisted Cartilage Reshaping for Reconstructive Surgery

UCI - Beckman Laser Institute and Medical Clinic

Thomas Milner, Ph.D.
J. Stuart Nelson, M.D., Ph.D.
Brian Wong, MD
Johannes DeBoer, Ph.D.

Glenn Edwards, Ph.D. Vanderbilt University
Emil Sobol, Ph.D. Center for Technological Lasers, Troitsk, Moscow Region

Objective: Design, construct, and test a prototype feedback control system to attain mechanically stable modified cartilage configurations.

Approach: Investigate the governing thermophysical mechanisms that determine the exposure-time and light-dosage values (t_e,D) required for successful cartilage reshaping at selected FEL wavelengths.

Payoff: Development of novel orthopedic, otolaryngologic, and plastic and reconstructive surgical procedures.

MACROPHAGE-TARGETED PHOTODYNAMIC REGULATION OF WOUND HEALING

Beckman Laser Institute, UC Irvine

1) Animal Models: PVA sponge implant in the rat; rabbit ear model of excisional wound healing; murine model of pulmonary fibrosis; peritoneal injury in rat (?); (Uptake/binding in macrophage, endothelial, fibroblast, and keratinocyte cells)

2) Clinical Applications:

- General mechanical/thermal damage to tissue structures from battlefield injuries
- Surgically-induced damage leading to adhesions, hypertrophic scarring, neuroma formation
- Intimal hyperplasia formation following vascular damage from mechanical injury and surgical interventions
- Repair of chronic injury/ulceration from infection or systemic disease

3) Milestone Chart:

'97
- Prepare and characterize photosensitizer-ligand conjugates (MGH).
- Quantitative photosensitizer-conjugate binding studies *in vitro*: (BLI).
- Cell imaging and localization studies *in vitro* and *in vivo*: (BLI).
- Cellular uptake studies: (MGH).
- Develop and introduce animal models to other sites: (Vanderbilt).

'98
- Evaluate PDT dose-response using cellular/biochemical endpoints in vitro and in vivo: (MGH).
- Evaluate PDT dose-response in vivo using morphological endpoints: (BLI).
- Correlate morphological and biochemical data to understand overall regulation mechanisms: (BLI, MGH and Vanderbilt).

- Specialized Equipment: Low-light level fluorescence microscopy with spectral and spatial resolution; image processing; In-vivo imaging using two photon excited microscopy, in vivo light dosimetry models, PDT sources.

MACROPHAGE-TARGETED PHOTODYNAMIC REGULATION OF WOUND HEALING

Beckman Laser Institute, UC Irvine

1) Contact: Bruce Tromberg, BLIMC

2) Key Personnel: Postdoctoral and Surgical Fellows (TBN)

3) Collaborators: Tayyaba Hasan, Wellman; Jeffrey Davidson, Vanderbilt

4) Project Objective: Regulate wound repair using macrophage-targeted photosensitizers and light.

5) Project Approach: Use cellular and pre-clinical animal models to:

- Develop and characterize Mϕ targeted sensitizers.
- Determine light activation parameters for full range of biological effects.

Vanderbilt: *Develop animal models and provide expert interpretation of histopath.*

Beckman: *Develop cellular and tissue imaging methods to quantify drug delivery, light dosimetry, and tissue damage parameters;*

Wellman: *Produce, characterize, and evaluate the biochemical efficacy of photosensitizer-ligand conjugates in cell and animal models.*

6) Payoff: Clinical technique offering selective regulation of tissue debridement *and* remodeling during wound repair:

- Suppress hyperplastic, fibrotic tissue growth during post-injury remodeling phase;
- Enhance tissue removal during post-injury debridement phase.

Laser Osteotomy Using the Free Electron Laser: Effects of Energy Mode on Bone Healing, Remodeling, and Implant Stability

George M. Peavy, D.V.M., Bahman Anvari Ph.D., J. Stuart Nelson, M.D., Ph.D. .
University of California - Irvine, Beckman Laser Institute and Medical Clinic

John T. Payne, D.V.M., MS, and James L. Tomlinson, D.V.M., MVSc,
University of Missouri - Columbia, College of Veterinary Medicine

Lou Reinisch Ph.D.
Vanderbilt University - Medical FEL Center

Waifung Cheong, Ph.D.
Stanford University - FEL Center

Objective: To define the most appropriate wavelength and delivery mode for laser ablation of bone tissue.

Approach: Work currently in progress is investigating wavelengths at bone absorption peaks to define an appropriate wavelength for use in bone ablation procedures. Following the selection of an optimum wavelength, its application for bone ablation will be further refined by defining the most appropriate delivery mode (pulse sequence) for application, and evaluating the concurrent application of dynamic cooling to reduce any thermal injury at the ablation site.

Payoff: Defining a laser wavelength, delivery mode and application approach that will allow a laser system to be developed for orthopedic procedures.

Laser Osteotomy Using the Free Electron Laser: Effects of Energy Mode on Bone Healing, Remodeling, and Implant Stability

Animal Models:

Rat Tibia - investigation of 3 different delivery modes (pulse sequences)
Rabbit Tibia - investigation of concurrent application of dynamic cooling
Canine Ulna - in-vivo evaluation of defined wavelength, delivery mode and possible application of dynamic cooling.

Clinical Applications: Orthopedic procedures, including joint replacement and reconstructive surgery.

Equipment/Task	1996	1997				1998			
	4	1	2	3	4	1	2	3	4
Define Wavelength	X	X	X						
Beam Time	30 hrs								
Decision Points			●						
Define Delivery Mode (pulse sequence)				X	X				
Beam Time VU-MFELC				30 hrs					
SU-FELC				16 hrs					
Decision Points					●				
Evaluate Dynamic Cooling			X		X	X			
Beam Time					30 hrs				
Decision Points			●			●			
In-Vivo Application					X	X	X	X	X
Beam Time						30 hrs			
Decision Points									●

Laser Applications For Wound Sterilization

George M. Peavy, D.V.M., and Bruce Tromberg, Ph.D.
University of California - Irvine, Beckman Laser Institute and Medical Clinic

Benjamin F. Edwards, Ph.D., James Carlson, Ph.D., Larry Galuppo, D.V.M., Bruce R. Madewell, D.V.M.
University of California - Davis, School of Veterinary Medicine

Eric Pope, D.V.M., MS, John N. Berg, D.V.M., Ph.D., Margaret A. Miller, D.V.M., Ph.D.
University of Missouri - Columbia, College of Veterinary Medicine

Kenneth E. Bartels, D.V.M., MS, Ernest L. Stair Jr., D.V.M., MS, Ph.D.,
Rebecca J. Morton, D.V.M., MS, Ph.D., Steven A Schafer, Ph.D., D. Thomas Dickey, D.V.M.
University of Oklahoma, College of Veterinary Medicine

Lou Reinisch Ph.D.
Vanderbilt University - Medical FEL Center

Objective: To evaluate the use of endogenous photochemical inactivation, selective photon absorption and chromophore enhanced photothermolysis as potential methods of sepsis control.

Approach: 1. Determine *in vitro* and then *in vivo* if endogenous photochemical compounds can be used for selective bactericidal activity.

2. Determine *in vitro* if specific bacteria have photon absorption peaks in the visual and infrared regions that are different than those for skin, muscle and blood. Determine *in vitro* if selective uptake of specific minerals can be used to enhance selective targeting of bacteria. Determine *in vivo* if specific wavelengths or the selective uptake of specific minerals by bacteria can be used to enhance selective targeting of bacteria for photothermolysis.

3. Determine *in vitro* if indocyanine green, indigo carmine, and carbon black can be used with commercially available solid state and diode laser systems to selectively kill bacteria. Determine *in vivo* if a dye chromophore and specific wavelength of laser light can be use for the selective thermolysis of bacteria without undue collateral soft tissue injury.

Payoff: Development of new methods for inactivating infectious agents.

Laser Applications For Wound Sterilization

Animal Models:

Mouse Abrasion Model
Rabbit Infected Wound Model

Clinical Applications: Sepsis control (wounds, burns, environmental decontamination)

Equipment/Task	1997				1998			
	1	2	3	4	1	2	3	4
Endogenous Photochemical Inactivation	X	X	X	X	X	X	X	
Beam Time (none needed)								
Decision Points				●			●	
Selective Photon Absorption	X	X	X	X	X	X	X	X
Beam Time (not yet determined)								
Decision Points				●			●	●
Chromophore Enhanced Photothermolysis	X	X	X	X	X	X	X	
Beam Time (none needed)								
Decision Points				●			●	

Title:	**Application of Free Electron Laser (FEL) in Bone Surgery**
Institution:	**Duke University**
Investigators:	**Longen Chen, PI** **James R. Urbaniak, Co-PI** **Anthony V. Seaber, Co-PI**
Collaborators:	**To be named**
Project Objective:	**Evaluation of infrared FEL as a tool for bone cutting**
Project Approach:	**Explore efficiency of bone cutting as a function of wavelength and power density** **Evaluate bone healing rate and quality compared with other bone cutting methods**
Project Payoff:	**Faster, stronger bone repair after FEL bone incision than with saw**

DukeFEL

Project title: Application of Free Electron Laser (FEL) in Bone Surgery

Institution: Duke University

Animal Model: Rat

Clinical Application: Bone incision for repair after trauma.
Replace other bone incision devices, because healing is faster and union is stronger.
Remove cement used with prior prostheses.

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Optimal laser parameters	→	→							
Healing Studies		→	→						
Beam time	4 hrs/wk	►	6 hrs/wk.						

↑ **Review bases for continued research**

Project title:	**Application of Free Electron Laser in Peripheral Nerve Surgery**
Institution:	**Duke University**
Investigators:	**Dr. Longen Chen, PI** **Dr. James R. Urbaniak, Co-PI** **Mr. Anthony V. Seaber, Co-PI**
Collaborators:	**To be named**
Project Objective:	**Test whether or not the FEL can make acceptable sections of peripheral nerve**
Project Approach:	**Section rat sciatic nerves - reapproximate them and do functional and histological studies of the reapproximated nerve**
Payoff:	**A much better method of sectioning the peripheral nerve in reparative/reconstructive surgery than now available**

Project title: **Application of Free Electron Laser in Peripheral Nerve Surgery**

Institution: **Duke University**

Animal Model: **Rat**

Clinical Application: **Peripheral nerve repair - trauma and reconstructive procedures**

Milestones

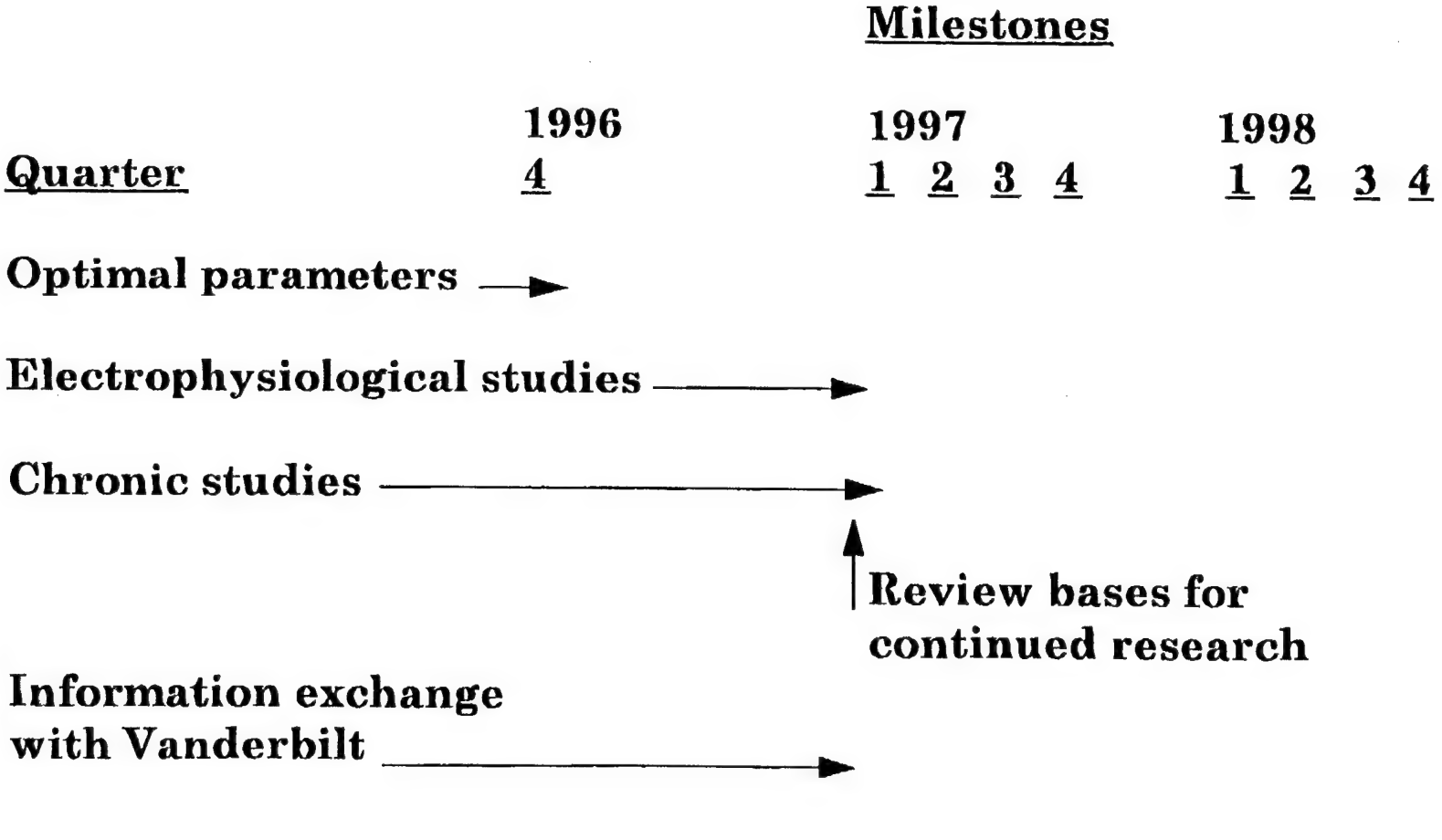
	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Optimal cutting parameters	→								
Functional recovery		→							
Analysis		→				→			
beam time:	4 hrs/wk.	→				6 hrs/wk.	→		

Project title:	**Parietal Cortex Lesions in the Rat**
Institution:	**Duke University**
Investigators:	**Blaine Nashold, Jr., PI** **Janice Ovelmen-Levitt, Co-PI** **Robert Pealstein, Co-PI** **Huaxin Sheng, Co-PI**
Collaborators:	**Michael Copeland, Vanderbilt**
Project Objective:	**Evaluate IR FEL as a surgical tool in the CNS**
Project Approach:	**Study, in the brain, FEL-induced lesion depth, collateral damage in both acute (4 hrs) and chronic (3 weeks) stages as a function of power density wavelength and number of laser pulses.**
Payoff:	**Lesions in the CNS which can be made with precision and with minimal collateral damage. Better than any method available today.**

Project title: Parietal Cortex Lesions in the Rat

Institution: Duke University

Clinical Application: Production of Drez lesions in the spinal cord for pain control and removal of epileptic foci



Project title:	**Free Electron Laser-Human Tissue (Skin) Interactions**
Institution:	**Duke University**
Investigators:	**Dr. Robert E. Clark, PI** **Dr. Shabnam Madani, Co PI**
Collaborators:	**Dr. Tom Flotte (MGH)**
Project Objective:	**Evaluate the FEL as a low-damage method for skin incision**
Project Approach:	**Using surviving human skin, establish optimal FEL parameters for low-damage skin incisions, assess the biological response of human skin to FEL incisions, and use miniature pigs to measure wound healing rates after FEL incisions**
Payoff:	**Low damage skin incisions - low inflammatory response**

Project title: Free Electron Laser-Human Tissue

Institution: Duke University

Animal Model: Miniature swine

Clinical application: Skin incision with low damage-precise removal of skin grafts with low damage

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Optimal parameters for linear cutting	→								
tissue staining standardization	→								
Immunohistology studies (human)	→								
Electron microscopy	→								
Miniature swine healing					→				
beam time → **4 hrs/wk.**	→								

Project title:	FEL Incision in Corneal Surgery
Institution:	Duke University
Investigators:	W. C. Fowler, PI John Rose, Co PI Alan D. Proia, Co PI
Collaborators:	Karen Joos (Vanderbilt)
Project Objective:	Evaluate the FEL operating in the ultra-violet as a tool for making corneal incisions
Project approach:	Cutting efficiency and collateral damage as a function of UV wavelength and power density will be measured in surviving pig cornea. This will be followed by long term corneal healing and stability of corrected cornea in rabbits. The final aspect of the study will utilize human blind eyes for refractive correction and healing rates.
Payoff:	Optimal ultraviolet wavelength and power density for corrective corneal surgery will be established.

Project title: FEL Incision in Corneal Surgery

Institution: Duke University

Animal Model: Surviving cornea from pig
New Zealand Rabbits

Human Studies: Final phase - 10 humans using blind eye

Clinical Application: Optimal corneal corrective surgery

Milestones

	1996	1997			1998			
Quarter:	4	1	2	3	4	1	2	3	4

Optimal UV FEL Parameters ——————→

Healing studies in Rabbits ——————→

Human blind eye studies ——————→

Beam time ——— **6 hrs/wk** ——→ **10 hrs/wk** ——→ **6 hrs/wk** ——→

DukeFEL

Project title:	**Three-Dimensional Energy Selective Micro-Computed Tomography**
Institution:	**Duke University**
Investigators:	**G. Allan Johnson**
Collaborators:	**Carey Floyd, Duke** **Larry Hedlund, Duke**
Project Objective:	**Development of a three-dimensional volumetric computed tomographic system for <u>in vivo</u> microscipy of biologic specimens.**
Project approach:	**A 1800 x 2300 element detector (experimental from GE) will be interfaced to a high-speed data aquisition system and configured to accomodate real-time projection x-ray microscopy. Energy and time selective computed tomography. Energy and time selective subtraction microradiography will then be added. Finally, cone beam projection reconstruction algorithm will be used for 3 D computed tomography and 3 D energy selective computed tomography.**
Payoff:	**Sequential <u>in vivo</u> 3 D tomography whole small animals such as rats with microscopic resolution will make possible use of the same animal for sequential microscopic studies. This will save large numbers of animals and valuable time.**

Project title: Three-Dimensional Energy Selective Micro-Computed Tomography

Institution: Duke University

Animal Model: Rat

Clinical Application: Animal testing of pharmacological agents, trauma models etc, will be faster, cheaper, use fewer animals

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Delivery of detector		→							
Construction of synchrotron X-ray beam line		→	→	→					
Real time X-ray projection microscopy				→	→	→	→		
Subtraction micro-radiography				→	→	→	→		
Algorithm development			→	→	→				
Beam time	8 hrs/wk	→	→	→	→	→	→	→	

Project title: Free Electron Laser Interaction with Ocular Tissues: A Surgical Benefit?

DukeFEL

Institution: Duke University

Investigators: Cynthia A Toth

Collaborators: K. Joos (Vanderbilt), D. Jansen, M. Frenz, A. J. Welch (U. of Tex, Austin), B. Rockwell, (Armstrong Laboratories) D. Katz (Duke), J. S. Nelson (Beckman)

Project Objective: Identify optimal ablation wavelength in the infrared which will induce minimal collateral damage and minimal tissue healing response in the posterior segment of the eye.

Project approach: Model collagen patches placed in vitreous of enucleated pig eyes will be used for wavelength and power density studies. This will be followed by whole animal studies (rabbit) to assess tissue response and compare with standard surgical and Er:YAG laser surgical incision in eyes which have induced scars. Fiber optic delivery will be required and perflubron perfusion to limit unwanted absorbtion will also be tested.

Payoff: Demonstration of low - damage removal of posterior segment scars. Use of perflubron to deliver power in tissue.

Project title: **Free Electron Laser Interaction with Ocular Tissues: A Surgical Benefit?**

Institution: **Duke University**

Animal Model: **Enucleated pig eyes**
Rabbit

Clinical Application: **Removal of pre-retinal scar and low damage posterior segment surgery of the eye**

Milestones

	1996	1997				1998
Quarter:	4	1	2	3	4	1
Enucleated pig	→	→	→	→		
Retinal motion sensor testing	→	→	→			
Testing of fiber optics at 2.94 μ	→	→	→			
Testing of OCT		→	→	→		
Rabbit acute and chronic studies		→	→	→	→	
Perflubron perfusion studies				→	→	
beam time	4 hrs/wk →	→	→	→	8 hrs/wk →	

Project title: **Exploration of Coherent Dark-Field Detection As a Means to Detect CBW Agents and Pathogens**

Institution: **Duke University**

Animal Model: **N/A**

Clinical Application: **Early warning - sensitive, reliable detection of CBW agents**

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Detection of Dark-Field signatures of model compounds	→	→	→	→					
Exploration of Dark-Field signatures of non-pathogenic bacteria		→	→	→	→	→	→	→	→
Exploration of scattering		→	→	→	→	→	→	→	→
Indoor range experiments						→	→	→	→
Beam time 4 hrs/wk	→	→	→	→	→	→	→	→	→

Project title: **Exploration of Coherent Dark-Field Detection As a Means to Detect CBW Agents and Pathogens**

Institution: **Duke University**

Investigator: **John M. J. Madey**

Project Objective: **Detection of CBW agents and pathogens under battlefield conditions**

Project approach: **Utilize the coherent, dark field scattered return between pulses of the infrared FEL to increase sensitivity of detection of absorbing chromophores**

Payoff: **Increase sensitivity of presently available sensing devices by order (s) of magnitude**

Project title	**Infrared Transmitting Fiber Optics for Delivery of Laser Radiation in the 2 to 9 μm Spectral Region**
Institution	**Duke/FDA**
Investigator	**R. W. Waynant**
Project Objective	**Development of fiber optics with lenses suitable for use in the mid-IR region**
Project approach	**Solid and hollow waveguides with suitable lenses will be tested for use with high peak pulsed power in the < 3.4 μ region. Concentric fiber optic-outside catheter systems will be tested for delivery of perflubron and deuterium oxide solutions to the field of irradiation.**
Payoff	**Delivery of high peak pulsed FEL power to surgical field through surgically useful fiber optic system.**

Project title **Infrared Transmitting Fiber Optics for Delivery of Laser Radiation in the 2 to 9 μm Spectral Region**

Institution **Duke University**

Animal Model **As per other investigators**

Clinical Application **Delivery of FEL power through suitably flexible fiber optics allows surgery in areas such as eyes which are not accessible with open beam optics.**

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Hollow waveguide at 2.94 μ	→								
Solid waveguide at 2.94 μ	→								
Lenses for 2.94 μ	→								
Hollow waveguide for 6.45 μ	→								
Concentric delivery system	→								
Beam time 6 hrs/wk	→								

Project title: **Biological X-Ray Analysis Using A FEL**

Institution: **Duke University**

Investigator: **E. A. Le Furgey, Co PI**
P. Ingram, Co PI

Project Objective:

(A.) Design, contruct and test x-ray fluoresence microscope using high brightness x-ray from mm wave FEL inverse Compton source
(B.) Improve on microprobe techniques currently available
(C.) Improve elemental sensitivity and spacial resolution of microprobe techniques

Project approach: **Using a special stage and x-ray optics, construct a a scanning electron microscope which can collect structural data (electron imaging) and elemental distribution data (x-ray microprobe) on the same sample.**

Payoff: **Demonstration of order of magnitude increases in sensitivity of microprobe elemental analysis on cellular and subcellular levels.**

Project title	**Biological X-Ray Analysis Using A FEL**
Institution	**Duke University**
***Animal Model*:**	**Rat; invertebrates**
Clinical Application	**Localization of toxic elements in cells-tracing toxic or indicator elements in food chain - CBW response in man**

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Fabrication of stage	→	→	→	→	→				
Construction of synchrotron x-ray beamline	→	→	→	→	→				
X-ray optic development	→	→	→	→	→	→	→	→	→
X-ray microprobe using synchrotron sources					→	→	→	→	→
Review bases for continued research		↑							
Beam time		**12 hrs/wk**	→	→	→	→	→	→	→

Project title: **Soft X-Ray Imaging of Living Cells**

Institution: **Duke University**

Investigator: **J. M. J. Madey, PI**
L. Johnson, G. Denbeaux

Project Objective: **To produce high resolution images of living cells**

Project approach: **Using quasicoherent 4 Å radiation from an undulator on the 1 GeV Duke Storage Ring, utilize the contrast between oxygen and carbon to make images of living cells by contact micrography on a photoresist and/or projection imaging on a high resolution CCD array.**

Payoff: **100 Å resolution images of living cells**

Project title	**Soft X-Ray Microscopy of Living Cells**
Institution	**Duke University**
Animal Model	**Invertebrates**
Clinical Application	**Soft X-ray microscopy will allow for the first time the overall structure of living cells (water still present) to be seen at high resolution. Disruption of water dependent cellular structures is a basic pathological response of all cells and protection from acute cellular damage will be greatly aided by information developed by this technique.**

Milestones

	1996	1997				1998			
Quarter	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
NIST undulator on beamline	→	→	→	→					
Beamline construction	→	→	→	→					
Wavelength and power measurements		→	→	→					
Exploration of contact micrography				→	→	→	→	→	
Exploration of projection micrography				→	→	→	→	→	
Beam time 8 hrs/wk	→	→	→	→	→	→	→	→	→

DukeFEL

Project title	**Studies on Multiphoton Dissociation of Small Molecules In the Gas Phase**
Institution	**Duke University**
Investigator	**K. D. Straub**
Collaborators	**A. Petrov, J. Chesnikov, Y. Molin (ICKC, Novosibirsk)**
Project Objective	**Explore the multiphoton reactions in small molecules in the gas phase in the mid-IR. Develop photosensitized destruction of toxic molecules by MPD.**
Project approach	**Optimal parameters for MPD of small molecules including coherence, wavelength, power and optical "chirp" in molecules such as formic acid, water, etc., are explored using mass spectrum analysis.**
Payoff	**Demonstration of effectiveness of FEL radiation for multi-photon chemistry at high pressure**

CHARGE FOR BREAKOUT GROUPS - 1

- DEFINE DETAILED RESEARCH SCHEDULES FOR NEXT 12 MO (EXPTS TO BE PERFORMED, ANIMALS, LOCATION, BEAM TIME . . .)
- I. D. POTENTIAL NEW/UNANTICIPATED TASKS ASSOCIATED W/ COLLABORATIONS OR SCHEDULES
- DEFINE 6 MON HORIZON OF ACCOMPLISHMENTS
- DEFINE ~~IR~~ 24 MON HORIZON OF ACCOMPLISHMENTS

- CONSIDER / SUGGEST OPPORTUNITIES FOR MINIMIZATION / SUBSTITUTION OF ANIMAL MODELS
  - TISSUE / CELL CULTURE
  - HUMAN / CLINICAL
  - OTHER (MARINE MODEL)

- SUGGEST WORKING GROUP REFINEMENTS (NEW GROUPS, COMBINED GROUPS

Single Micropulse Ablation/Stanford University

Point of Contact: H. Alan Schwettman, Michael D. Fayer

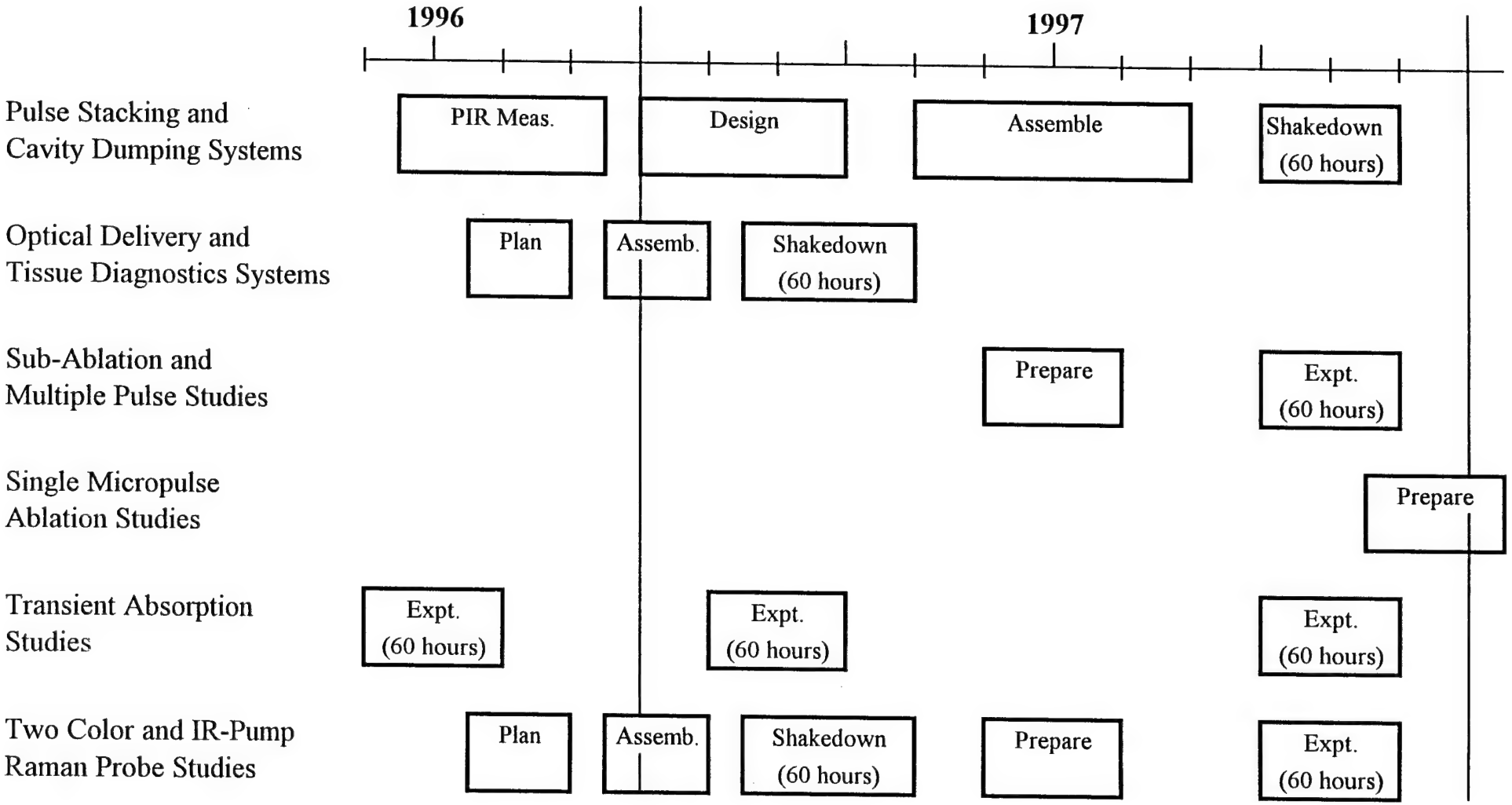
Collaborators: Norman Nishioka, M.D., Wellman Laboratories, M.G.H.
Kristen A. Peterson, New Mexico State University

Project Objectives: Characterize tissue ablation for ultra short infrared optical pulses.

Project Approach: By pulse stacking and focusing the FEL beam, the ablation threshold for tissue can be exceeded by a significant margin in a single micropulse. Optical transmission measurements, real-time thermal-mechanical measurements and histological analysis will be used to characterize the ablation process. Vibrational dynamics techniques (transient absorption, two color pump-probe, and IR pump/Raman probe) will be used to study the energy redistribution process.

Payoff: Guidance in selecting laser parameters for surgery applications.

Single Micropulse Ablation/Stanford University
Milestone Chart



Scanning Near Field Infrared Microscopy/Stanford University

Point of Contact: Todd I. Smith

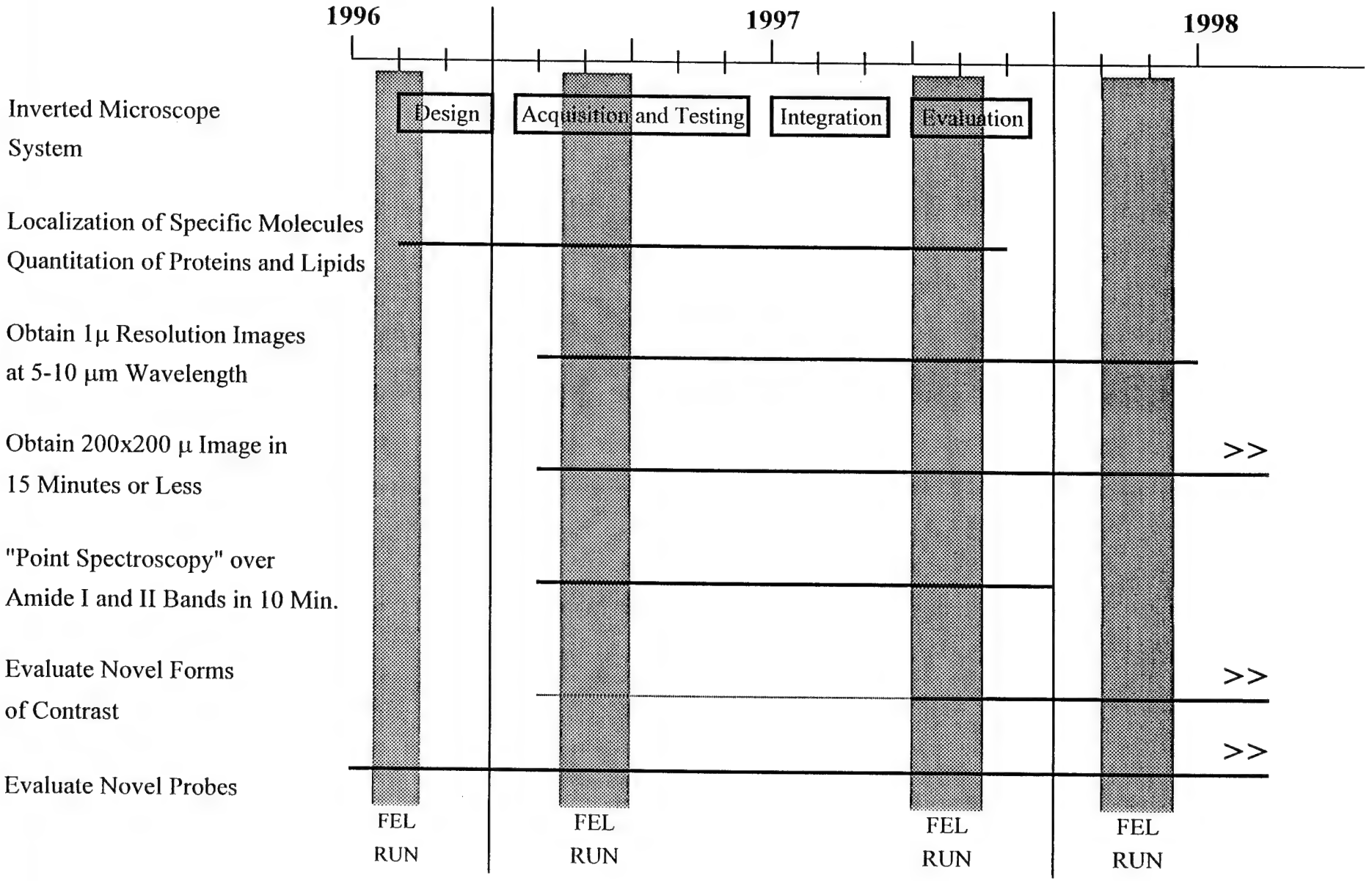
Collaborators: Shyamsunder Erramilli, Mi K. Hong; Boston University

Project Objectives: Develop scanning near field microscopy as an imaging tool for bio-medical applications.

Project Approach: A prototype scanning near field infrared microscope using infrared transmitting fibers has been developed in a collaboration between Stanford and Boston Universities. An improved version of the microscope will be constructed and used to demonstrate high resolution spectroscopic imaging of biological samples.

Payoff: A new imaging technique may help understand a variety of medical conditions.

Scanning Near Field Infrared Microscopy/Stanford University
Milestone Chart



Scanning Near Field Infrared Microscopy/Stanford University

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Payoff: A new imaging technique may help understand a variety of medical conditions.

Soft Tissue Surgery

Project Title:	FEL Applications for Neurosurgery/Tissue Interactions and Wound Healing in the Upper Respiratory Tract/FEL Welding Procedure Development and Wound Healing in Ocular Tissues/Molecular Biophysics
Institution:	Vanderbilt University
P.I.'s:	Michael Copeland/Gaelyn Garrett/Karen Joos/Glenn Edwards
Collaborators:	Vivien Casagrande, Jeff Davidson, and James McKanna. Rox Anderson, Tom Flotte, and Cynthia Toth.
Project Objective:	Conduct animal studies necessary to justify FEL applications to human surgery. Elucidate mechanisms governing ablation.
Project Approach:	Animal models have been identified for each medical specialty to pursue clinical and surgical applications of FEL tissue ablation and FEL tissue welding. Surgical procedures have been identified for initial applications. Beam delivery issues are being addressed by collaborating physicists and biomedical engineers. Wound healing issues are being addressed by collaborating biomedical scientists.
Payoff:	Potential for improved medical care based on novel FEL-based protocols.

Project Title: FEL Applications for Neurosurgery/Tissue Interactions and Wound Healing in the Upper Respiratory Tract/FEL Welding Procedure Development and Wound Healing in Ocular Tissues

Institution: Vanderbilt University

Animal Models:

FEL Applications for Neurosurgery
canine, pig

Tissue Interactions and Wound Healing in the Upper Respiratory Tract
canine

FEL Welding Procedure Development and Wound Healing in Ocular Tissues
rabbits, monkeys, and pigs

Clinical Applications:

FEL Applications for Neurosurgery
corticotomy
brain debridement
mass lesion resection
quantitative measurement of brain injury

Tissue Interactions and Wound Healing in the Upper Respiratory Tract
surgical treatment of subglottic stenosis (SGS)
surgical treatment of posterior glottic scar (PGS)
minimize hypertrophic scar formation

FEL Welding Procedure Development and Wound Healing in Ocular Tissues
retinal welding
repair of ocular lacerations

Milestones

	1997				1998				1999	
	1	2	3	4	1	2	3	4	1	2
Neurosurgery	data analysis			IRB application		Human application				
	endovascular (flow chamber)					endovascular (animal experiments)				
Otolaryngology	SGS/PGS----------									
Ophthalmology:										
laser parameter identification			X	X						
rabbit studies				X	X	X				
monkey studies									X	X

Hard Tissue Surgery

Project Title:	Selective Modification of Materials/Hard-Tissue Modification and Wound Healing Mechanisms/Molecular Biophysics
Institution:	Vanderbilt University
P.I.'s:	Norman Tolk/Richard Haglund/Glenn Edwards
Collaborators:	Jeff Davidson, Hee Park, Tom Milner
Project Objective:	Elucidate mechanisms, applications to dental surgery and biomaterials, cartilage reshaping
Project Approach:	Investigate mechanisms of hard-tissue ablation, hydroxyapatite deposition, and cartilage reshaping with the aim of developing clinical applications.
Payoff:	Basic research with the potential for enabling biomedical research and clinical applications

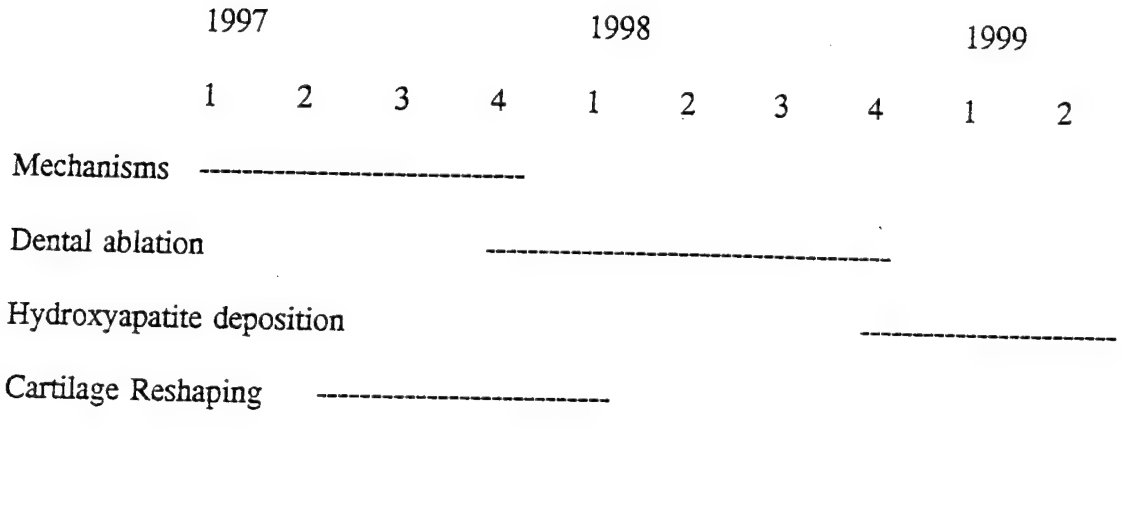
Project Title: Selective Modification of Materials/Hard-Tissue Modification and Wound Healing Mechanisms/Molecular Biophysics

Institution: Vanderbilt University

Animal Models: TBN

Clinical Applications: Dental surgery, biocompatibility, and cartilage surgery

Milestones



Diagnostics/Imaging

Monochromatic X-ray Project

Vanderbilt University FEL Center

P.I. - Frank Carroll, M.D.

Key personnel:
James Waters, Ph.D.
Weiwei Clark, Ph.D.
Charles Brau, Ph.D.
Robert Traeger
Ron Price, Ph.D.
David Pickens, Ph.D.

Major collaborators:
James Nelson, M.D.
University of Washington Seattle
Todd Smith, Ph.D.
Stanford University
FDA/LLNL - TOF detectors

Objective: - Production and Use of Monochromatic X-rays for Diagnosis and Treatment in Medicine

Approach: - Compton Scatter, mosaic crystals, standard imaging,Time-of-flight and phase imaging

Payoff: - Earlier and more accurate diagnosis of breast cancer, as well as improved imaging in all facets of medicine. Improved therapy.

Monochromatic X-ray Project

Vanderbilt University FEL Center

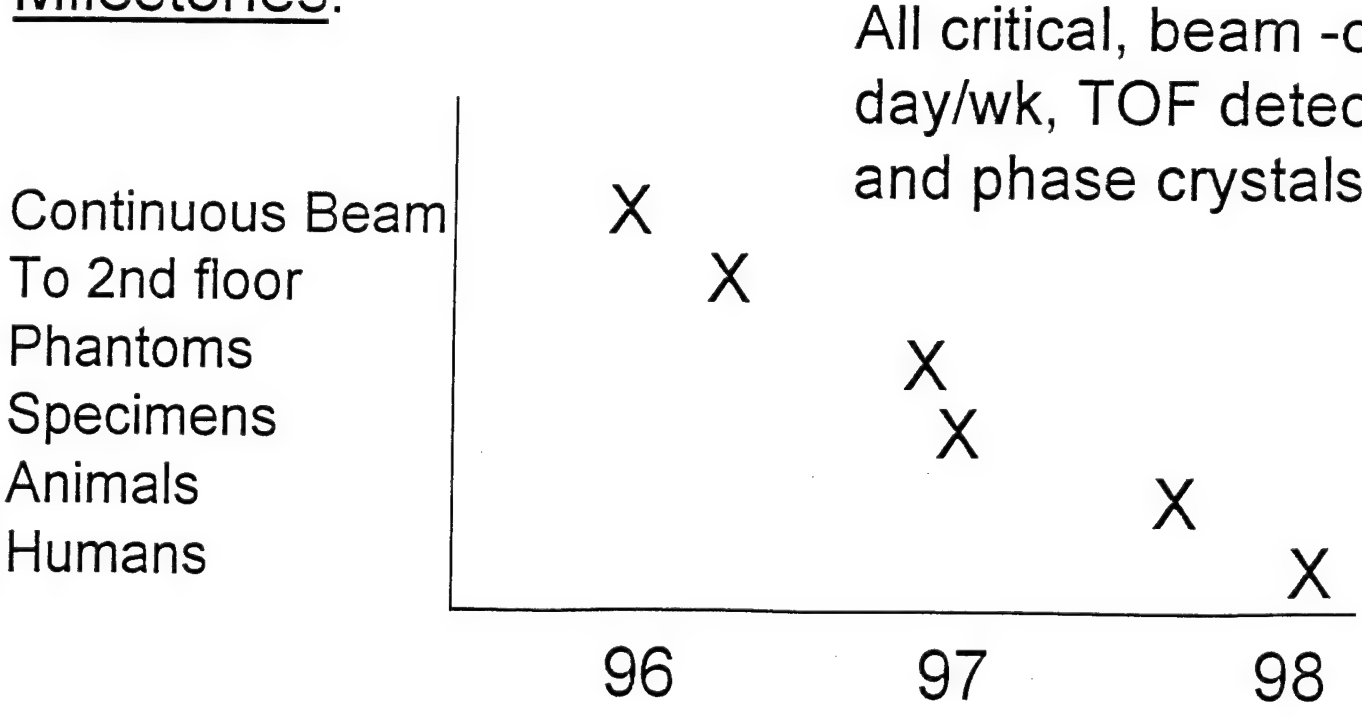
Models:

Tissue - Excised specimens up to whole breasts.
Animal - Mouse (rabbit) - tumor/ChemoradioRx
Dead animals - tissue injuries/trauma

Clinical Applications:

Breast cancer - Dx and Rx. Improved Sens./Spec.
Other X-ray applics. - marked improvement S/N

Milestones:



Tissue Welding

Project Title:	Molecular Biophysics/FEL Welding Procedure Development and Wound Healing in Ocular Tissues
Institution:	Vanderbilt University
P.I.'s:	Glenn Edwards/Karen Joos/Vivien Casagrande
Collaborators:	Jeff Davidson
Project Objective:	Pursue observation of FEL induced photo-association of protein as potential mechanism for tissue welding/develop clinical procedures in ophthalmology
Project Approach:	The mechanism for the photo-association will be established by biophysical investigations. Clinical procedures will be developed in ophthalmology. Physiological consequences will be monitored by cell biologists. Beam delivery issues are being addressed by collaborating physicists and biomedical engineers.
Payoff:	The potential demonstration of IR photoproducts. Non-contact tissue welding.

Project Title: Molecular Biophysics/FEL Welding Procedure Development and Wound Healing in Ocular Tissues

Institution: Vanderbilt University

Animal Models: FEL Welding Procedure Development and Wound Healing in Ocular Tissues
rabbits, monkeys, and pigs

Clinical Applications: retinal welding
repair of ocular lacerations

Milestones

	1997				1998				1999	
	1	2	3	4	1	2	3	4	1	2
mechanisms	X	X								
beam delivery	X	X	X	X						
laser parameter identification				X	X					
rabbit studies					X	X	X			
monkey studies									X	X
two-shifts per week										

Wound Healing-Cell Biology/Vanderbilt

Jeff Davidson, Ph.D. *Cutaneous Wound Repair*	Vivien Casagrande, Ph.D. *Ocular Tissue Welding*	Jim McKanna, Ph.D. *Wound Healing and Regeneration in Neural Tissues*
Lillian B. Nanney, Ph.D. Jeff Whitsitt, M.D.	Karen Joos, M.D., Ph.D. Jin Shen, Ph.D.	Michael Copeland, M.D., Ph.D.
Collaborators		
Wound Debridement - Nishioka/Wellman Gene Therapy - Flotte/Wellman Skin Resurfacing - Anderson/Wellman Haglund/Vanderbilt Wound Healing - Reinisch/Vanderbilt Clark/Duke Macrophage PDT - Tromberg/Beckman Hasan/ Wellman	Ocular tissue welding - Edwards/VU Ocular histology -Shetlar/VU; Toth/Duke Glial/neural response - McKanna/VU Collagen remodeling - Davidson/VU	Phagocyte types/responses - Shepherd/VU Microglia:CNS damage -Joos,Copeland/VU Sciatic regeneration - Zealar/VU Microglia:Optic nerve regeneration -Joos, Casagrande/VU
Objectives		
Ablation vs. wavelength, pulse rate, fluence Incision vs. wavelength, pulse rate, fluence Chemical burn debridement Collagen remodeling Gene therapy of wounds/skin Macrophage modulation	Retinal welding vs. laser parameters Scleral welding vs. laser parameters Corneal welding vs. laser parameters Glial responses vs. laser parameters Neuronal responses vs laser parameters Collagen remodeling	Glial responses vs. laser parameters CNS damage vs FEL and other surgeries Phagocytes in sciatic nerve regeneration Phagocytes in optic nerve damage Microglia in animal models of CNS surgery
Approach		
Biochemical, histological, and biomechanical evaluation of wound sites Biochemical model of laser-collagen interactions: x-links, 2° structure FEL/conventional laser photoacoustics for DNA transfection of therapeutics PDT manipulation of macrophage function in wound models	FEL welding of detached retina Quantitative image analysis FEL welding of non-retinal ocular lacerations Immunocytochemical evaluation of retinal/ocular damage FEL repair/welding parameters	FEL and other lesions to sciatic and optic nerves Immunohistochemical identification of microglia and macrophages Quantitative image analysis
Payoffs		
Develop therapeutic FEL applications Validate, at a mechanistic level, the role of the FEL as a surgical and medical device	Therapeutic FEL applications to ocular surgery Novel tissue welding protocols using the FEL Objective evaluation of retinal/ocular damage Better understanding of neural tissue response to ocular damage and repair	Objective evaluation of CNS damage Identity and lineage of CNS phagocytes Evaluate ± influences of FEL parameters in CNS surgery Long term: promote CNS healing and regeneration

Wound Healing-Cell Biology/Vanderbilt

Cutaneous Wound Repair	*Ocular Tissue Welding*	*Wound Healing and Regeneration in Neural Tissues*
Jeffrey M. Davidson, Ph.D. Lillian B. Nanney, Ph.D. Jeff Whitsitt, M.D.	Vivien Casagrande, Ph.D. Karen Joos, M.D., Ph.D. Jin Shen, Ph.D.	Jim McKanna, Ph.D. Michael Copeland, M.D., Ph.D.

Animal Models

Tissue Ablation - Rabbit/Pig	Initial welding experiments: - cadaveric human/porcine eyes	Sciatic nerve - rat
Incisional Repair - Rat/Pig	Retinal detachment - rabbit/monkey	Optic nerve - rat, rabbit, monkey
Chemical Burn Debridement - Rat/Rabbit	Non-retinal ocular tissue - rabbit/monkey	Brain incisions and ablation - rat,dog
Macrophage PDT - Rat		

Clinical Applications

Plastic Surgery	Ocular surgery	Neurology and neurosurgery
Dermatologic Surgery	Plastic surgery	Ophthalmology
Burn care	Future - modulation of glial/neural responses	
Chronic wounds		
Skin resurfacing		
Inflammatory disease		

Milestones

Quarter	1/97	2/97	3/97	4/97	1/98	2/98	3/98	4/98	1/99	2/99
Task										
Ablation	→	→	→	→						
Incision	→	→	→	→	→	→	→	→	→	
Collagen denaturation			→	→	→	→	→	→		
Gene Therapy and Wound Healing			→	→	→	→	→	→	→	→
Macrophage PDT				→	→	→	→	→	→	→
CNS phagocyte types	→	→	→	→	→	→	→			
Sciatic nerve		→	→	→	→	→				
Optic nerve			→	→	→	→	→			
Glial responses in incision and ablation		→	→	→	→	→	→	→	→	→
Retinal detachment	→	→	→	→	→	→	→	→	→	→
Cellular responses vs. laser parameters			→	→	→	→	→	→	→	→
Scleral welding			→	→	→	→	→	→	→	→
Corneal welding	→	→	→	→	→	→	→			
Collagen remodeling			→	→	→	→	→	→	→	→
Equipment										
Beam Time, shifts/week	3	3	3	4	4	4	4	4	4	4

Core Operations/Vanderbilt University

Contacts : Bill Gabella also Marcus Mendenhall, Rick Grant, John Kozub, Ed Mone, Scott Storms

Objective : Increase quality of hours delivered to users, improve machine diagnostics, understand and make more reliable FEL tuning

Approach : Add diagnostics where feasible, study FEL tuning

Payoff : Better scientific results, quicker better tuning

Reliability Improvements/Vanderbilt University

Contacts : Bill Gabella and Operations Group

Collaborators : Bob Traeger (X-Ray Group), Bob Gardenghi, Myron Wheeler

Objective : Improve FEL reliability, especially the pulsed power system, study/increase FEL laser power

Approach : Hired consultants from industry, implementing a plan of "basics" (modulator air cooling, clean transformer oil, etc)

Payoff : Less downtime due to improved components, enhanced performance, more time for other operational issues

Beam Delivery/Vanderbilt University

Contacts : Marcus Mendenhall, Glenn Edwards, Terry King, Jin Hui Shen

Objective : Deliver beam to the human operating rooms, to the bullpen labs, and into patients and subjects; delivery devices for surgical application

Approach : Nearly straightforward extension of current IR transport system; non-articulated arm delivery systems

Payoff : Human patient procedures, more power into/onto the subject

Research to Develop Biomedical Applications of Free Electron Laser Technology

Revised Work Statement for 1997-98

John A. Parrish, M.D.
Principal Investigator, Wellman Laboratories of Photomedicine

The proposed work and budget for the Wellman Laboratories have been revised in accordance with the recommendations of the review panel. We are committed to accelerating the efforts to realize near-term medical payoffs and expanding our collaborations with the other MFEL Centers. We view our efforts as an integrated program of basic and applied research with the belief that an understanding of the mechanisms of laser-tissue interactions will permit better development of diagnostic and therapeutic applications. In order to facilitate the development of FEL applications and to foster our interactions with the FEL centers, we are planning to fund investigators at the FEL centers.

The revised plan will include the following sections from the original proposal:

A. Wound Healing
   1. Photoimmunotherapy for the local control of sepsis
   2. Treatment and diagnosis of chemical burn injury
   3. Macrophage targeted PDT regulation of wound healing
   4. Stress wave enhanced gene therapy for wound healing
B. Light-activated tissue repair
C. Spatially confined pulsed laser effects
   1. MIcroparticle targetting
   2. FEL-generated evanescent wave interactions and Development of evanescent-wave FEL scalpel
   3. Pulsed laser reversal of cerebral artery vasospasm
D. Effects of UVFEL radiation on biological molecules
E. Tissue effects of laser-induced stress waves
   1. In vivo applications
   2. Unipolar laser-induced tensile waves
   3. Influence of temporal pulse structure and wavelength on the response of tissue to mid-IR FEL laser irradiation.

Wellman laboratories of Photomedicine

Project Title:	Photoimmunotherapy for the Local Control of Sepsis
Principal Investigator:	Tayyaba Hasan, Ph.D.
Key Personnel:	Michael Hamblin, Ph.D. Jaimie Miller, B.S.
Collaborators:	Jeffrey Davidson, Vanderbilt David Benaron, Stanford
Project Objective:	To establish the role of local sepsis control in wound healing by bacteria using antibody/peptide targeted sensitizers
Project Approach:	Photosensitizer conjugate syntheses and testing *in vitro* to establish efficacy parameters. These will then be tested in an infected wound model *in vivo*.
Payoff:	This study is expected to provide a means of rapid sterilization of infected wounds so as to lead to accelerated wound healing

Project Title:	Photoimmunotherapy for the Local Control of Sepsis
Animal Model:	Mouse skin incisional model
Tasks:	1. Synthesize and characterize conjugates 2. In vitro uptake by bacteria and mammalian cells 3. In vitro photoinactivation of P. aerug. 4. In vitro photoinactivation of E. coli 5. Optimize photoinactivation parameters in vitro 6. In vivo mouse model - local administration 7. In vivo mouse model - systemic administration 8. Optimize photoinactivation parameters in vivo

Milestone Chart:

	1997			
Task	1	2	3	4
1	X	X		
2	X	X	X	
3		X	X	X
4			X	X

	1998			
Task	1	2	3	4
5	X	X		
6	X	X	X	X
7			X	X
8			X	X

Wellman laboratories of Photomedicine

Project Title:	Macrophage Targeted Photodynamic Regulation of Wound Healing
Principal Investigator:	Tayyaba Hasan, Ph.D.
Key Personnel:	Michael Hamblin, Ph.D. Norah Chen, B.S. Nedret Altiok, M.D., Ph.D.
Collaborators:	Bruce Tromberg, Backman Jeffery Davidson, Vanderbilt
Project Objective:	Demonstrate the photosensitized regulation of macrophage function for the acceleration of wound healing and the inhibition of adhesion formation.
Project Approach:	Targeting of photosensitizer conjugates to different macrophage receptors so as to elicit appropriate macrophage function modulation.
Payoff:	Wounds in the aged population or diabetics are often slow to heal. Battlefield injuries may also have wounds that are slow to heal due to infection or stress. Accelerated wound healing would be beneficial in both of these contexts. Normal surgical procedures or battlefield injuries may lead to adhesions which is often a cause of delayed recovery. These studies are aimed at reducing adhesion formation due to trauma.

Project Title:	Macrophage Targeted Photodynamic Regulation of Wound Healing
Animal Model:	Rat incisional model Rabbit ear model Rat intra-abdominal adhesion model
Tasks:	1. Synthesize and characterize targeting moeities 2. Uptake and imaging in cells 3. In vitro photosensitization cytokine release and cytotoxicity from macrophages 4. Photosensitized cytokine release and cytotoxicity of companion cells 5. Photosensitized growth and migration of companion cells 6. Photosensitized modulation of wound healing in the rat incisional model 7. Photosensitized modulation of abdominal adhesion model 8. Photosensitized modulation in rabbit ear ulcer model

Wellman Laboratories of Photomedicine

Project Title:	Stress wave enhanced gene therapy for wound healing
Principal Investigator:	Thomas J. Flotte, M.D.
Key Personnel:	Apostolos Doukas, Ph.D. Shun Lee, Ph.D.
Collaborators	Jeffrey M. Davidson, Vanderbilt
Project Objective:	To demonstrate that laser-induced stress-wave assisted gene therapy can accelerate wound healing
Project Approach:	The approach will be use to laser-induced stress-waves to deliver appropriate genes to create transient expression of TGF-ß1 in full thickness skin incisions as a means of enhancing the rate of wound repair.
Payoff:	A new method for molecular delivery that may be used for a variety of applications such as decreased time for recovery from wounds. Development of new approach for drug delivery which may result in new classes of drugs.

Project Title:	Stress wave enhanced gene therapy for wound healing
Animal Models:	Sprague-Dawley rat model of healing of skin incisions
Clinical applications:	Improved healing of acute wounds and non-healing ulcers
Milestones	Demonstration molecular delivery into the skin Demonstration of expression of gene products Demonstration of increased healing

Wellman Laboratories of Photomedicine

Project Title:	Influence of Temporal Pulse Structure and Wavelength on the Response of Tissue to Mid-IR FEL Irradiation
Principal Investigator:	Norm Nishioka, M.D.
Collaborator:	Alan Schwettman, Stanford
Project Objective:	Determine the relative influence of wavelength and pulse structure on tissue mechanical response and ablation dynamics Assess the diagnostic utility of tissue mechanical response
Project Approach:	Simultaneously measure the stress, displacement and temperature response of tissue to both ablative and subablative laser pulses for various wavelengths and pulse durations Detailed microscopic assessment of ablation craters using light and electron microscopy Develop theoretical models of tissue response Explore whether tissue mechanical responses to sub-ablative doses of laser irradiation provide useful diagnostic information about the tissue
Payoff:	Bloodless, efficient laser debridement and grafting with optimized rate of healing Decontaminate chemical/biological skin surface warfare agents Evaluate healing outcome for burns of indiscriminate depths

Project Title:	Influence of Temporal Pulse Structure and Wavelength on the Response of Tissue to Mid-IR FEL Irradiation
Beam Time:	~40 hours 2.95, 4.7, 5.99, 6.45, 6.75, 8.2, 10.6 μm 1-30 μJ, micropulses (singly, stacked or in sequence) Spot size: ~100 μm

Wellman laboratories of Photomedicine

Project Title:	FEL-Generated Refracted and Evanescent Waves for Surgery
Principal Investigator:	R. Rox Anderson, M.D.
Key Personnel:	Charles Lin, Ph.D. Ycov Domankevitez Brett Hooper, Ph.D.
Project Objective:	Understand, design, and implement a new class of contact laser surgery devices
Project Approach:	Determine the practical range of control over depth of optical penetration and tissue interaction, which can be obtained by varying refraction angle Characterize primary damage to soft tissues for e-wave and refracted FEL macropulses at wavelengths absorbed primarily by water Ablate tissue with FEL-generated evanescent waves at the margin of optical waveguides Build and test prototype FEL-pumped tissue ablation tools a. Contact surgery with e-wave and refracted beam b. Precise intra-luminal ablation tool
Payoff:	A new class of contact, pulsed laser surgical tools should come from this project, including better control over FEL tissue ablation.

Project Title:	FEL-Generated Refracted and Evanescent Waves for Surgery
Animal Models:	Porcine artery, skin and cornea
Milestones/ decision points	Demonstration of ablation efficiency sufficient for surgical practicality Demonstration of rough tissue surface smoothing Demonstration of silica devices for e-wave and refraction Demonstration of ablation at a waveguide-tissue interface Fabrication of prototype surgical device
FEL Beam time	1-2 days/week Macropulse energy at 2.7 μm (ideally, of at least 10 mJ)

Wellman laboratories of Photomedicine

Project Title:	Treatment and Diagnosis of Chemical Burn Injury
Principal Investigator:	Norm Nishioka, M.D.
Collaborator:	Jeff Davidson, Vanderbilt
Project Objective:	Compare the FEL and CO_2 laser pulses for debriding chemical burns Assess the accuracy of ICG fluorescence for evaluating the depth of chemical burns
Project Approach:	Create chemical burns in porcine skin using intradermal injections of Adriamycin Evaluate depth of burns with ICG fluorescence Debride using 6.45 μm FEL and 10.6 μm CO_2 Evaluate graft-take and rate of healing
Payoff:	Bloodless, efficient laser debridement and grafting with optimized rate of healing Decontaminate chemical/biological skin surface warfare agents Evaluate healing outcome for burns of indiscriminate depths

Project Title:	Treatment and Diagnosis of Chemical Burn Injury
Animal Models:	Adriamycin burns in porcine skin
Clinical Applications:	None planned
Milestone Chart:	Work in progress
Beam Time:	OR time: ~18 hours, Beam Time: ~6 hours 6.45 μm FEL for debriding burns Max. energy, Max. Rep. Rate Spot size: TBD

Wellman Laboratories of Photomedicine

Project Title:	Light-activated tissue repair
Principal Investigator:	R. Rox Anderson, M.D. Irene E. Kochavar, Ph.D.
Key Personnel:	David Lin, Ph.D. Bobby Redmond, Ph.D.
Project Objective:	Develop dye-mediated enhancement of pulsed laser photothermal tissue repair and compare to conventional suture repairs in skin and tendon. Develop a series of molecular crosslinking systems for type I collagen and test in vitro repair of connective tissues.
Project Approach:	Use of a tissue-binding dye, to provide (a) selective absorption of deeply penetrating laser light for local heating, (b) a local monitor of temperature and/or collagen unwinding used to control laser pulse energy, and (c) the option of photosensitized crosslinking of the weld enhanced strength. Design and synthesize bifunctional collagen cross-linking at fiber cleavage site. Investigate and optimize the efficacy of photochemical crosslinking via singlet oxygen, electron transfer, and free radical mechanisms.
Payoff:	Light-activated tissue repair provides hemostasis, precision, speed, strength, ability to seal against fluid leaks, compatibility with endoscopic surgery, and lack of foreign body response. Civilian and military personnel suffering from trauma or wounds may benefit from this alternative to conventional suture repairs.

Project Title:	Light-activated tissue repair
Animal Model:	Pig skin and rabbit achilles tendon models
Clinical Appl.	Rapid, sutureless repair of connective tissue.
Tasks:	1. Study dye fluorescence as a local monitor of temperature and/or collagen unwinding used to control laser pulse energy 2. Investigate singlet oxygen and electron transfer mechanisms for collagen crosslinking 3. Determine the efficacy of photochemically generated free radicals for inducing crosslinks. 4. Design and synthesize bifunctional collagen-targeted photoactivators for specific localizaton of collagen crosslinking at fiber cleavage site. 5. In vivo testing of photothermal welding using pig skin and rabbit achilles tendon as model connective tissues.

CHARGE FOR BREAKOUT GROUPS - 1

- DEFINE DETAILED RESEARCH SCHEDULES FOR NEXT 12 MO (EXPTS TO BE PERFORMED, ANIMALS, LOCATION, BEAM TIME . . .)
- I. D. POTENTIAL NEW/UNANTICIPATED TASKS ASSOCIATED W/ COLLABORATIONS OR SCHEDULE
- DEFINE 6 MON HORIZON OF ACCOMPLISHMENTS
- DEFINE 12 & 24 MON HORIZON OF ACCOMPLISHMENTS

- CONSIDER / SUGGEST OPPORTUNITIES FOR MINIMIZATION / SUBSTITUTION OF ANIMAL MODELS
  - TISSUE / CELL CULTURE
  - HUMAN / CLINICAL
  - OTHER (MARINE MODEL)

- SUGGEST WORKING GROUP REFINEMENTS (NEW GROUPS, COMBINED GROUPS

Laser-Assisted Cartilage Reshaping for Reconstructive Surgery

UCI - Beckman Laser Institute and Medical Clinic

Animal Models: Selected ex-Vivo cartilage harvested from porcine, rabbit, and chicken animals

Clinical Applications: Surgical correction of auricular and nasal deformities, reconstruction of tracheal and laryngeal defects

Equipment/Task	1997				1998			
	1	2	3	4	1	2	3	4
Penetration Depth/Wavelength (Infrared Detection System)	x	x	x	x				
Catalytic Techniques (Spray Cooling, Electric Field, Geometry)	x	x	x	x	x	x		
Optimal Dose-Exposure Times (Beam scanning system, strength measurement)	x	x	x	x	x	x		
Feedback System (Optical and/or Thermal)			x	x	x	x	x	x

Laser-Assisted Cartilage Reshaping for Reconstructive Surgery

UCI - Beckman Laser Institute and Medical Clinic

Thomas Milner, Ph.D.
J. Stuart Nelson, M.D., Ph.D.
Brian Wong, MD
Johannes DeBoer, Ph.D.

Glenn Edwards, Ph.D. Vanderbilt University
Emil Sobol, Ph.D. Center for Technological Lasers, Troitsk, Moscow Region

Objective: Design, construct, and test a prototype feedback control system to attain mechanically stable modified cartilage configurations.

Approach: Investigate the governing thermophysical mechanisms that determine the exposure-time and light-dosage values (t_e,D) required for successful cartilage reshaping at selected FEL wavelengths.

Payoff: Development of novel orthopedic, otolaryngologic, and plastic and reconstructive surgical procedures.

MACROPHAGE-TARGETED PHOTODYNAMIC REGULATION OF WOUND HEALING

Beckman Laser Institute, UC Irvine

1) Animal Models: **PVA sponge implant in the rat; rabbit ear model of excisional wound healing; murine model of pulmonary fibrosis; peritoneal injury in rat (?); (Uptake/binding in macrophage, endothelial, fibroblast, and keratinocyte cells)**

2) Clinical Applications:

- **General mechanical/thermal damage to tissue structures from battlefield injuries**
- **Surgically-induced damage leading to adhesions, hypertrophic scarring, neuroma formation**
- **Intimal hyperplasia formation following vascular damage from mechanical injury and surgical interventions**
- **Repair of chronic injury/ulceration from infection or systemic disease**

3) Milestone Chart:

'97
- **Prepare and characterize photosensitizer-ligand conjugates (MGH).**
- **Quantitative photosensitizer-conjugate binding studies *in vitro*: (BLI).**
- **Cell imaging and localization studies *in vitro* and *in vivo*: (BLI).**
- **Cellular uptake studies: (MGH).**
- **Develop and introduce animal models to other sites: (Vanderbilt).**

'98
- **Evaluate PDT dose-response using cellular/biochemical endpoints in vitro and in vivo: (MGH).**
- **Evaluate PDT dose-response in vivo using morphological endpoints: (BLI).**
- **Correlate morphological and biochemical data to understand overall regulation mechanisms: (BLI, MGH and Vanderbilt).**

- **Specialized Equipment: Low-light level fluorescence microscopy with spectral and spatial resolution; image processing; In-vivo imaging using two photon excited microscopy, in vivo light dosimetry models, PDT sources.**

MACROPHAGE-TARGETED PHOTODYNAMIC REGULATION OF WOUND HEALING

Beckman Laser Institute, UC Irvine

1) Contact: Bruce Tromberg, BLIMC

2) Key Personnel: Postdoctoral and Surgical Fellows (TBN)

3) Collaborators: Tayyaba Hasan, Wellman; Jeffrey Davidson, Vanderbilt

4) Project Objective: Regulate wound repair using macrophage-targeted photosensitizers and light.

5) Project Approach: Use cellular and pre-clinical animal models to:

- Develop and characterize Mϕ targeted sensitizers.
- Determine light activation parameters for full range of biological effects.

Vanderbilt: *Develop animal models and provide expert interpretation of histopath.*

Beckman: *Develop cellular and tissue imaging methods to quantify drug delivery, light dosimetry, and tissue damage parameters;*

Wellman: *Produce, characterize, and evaluate the biochemical efficacy of photosensitizer-ligand conjugates in cell and animal models.*

6) Payoff: Clinical technique offering selective regulation of tissue debridement *and* remodeling during wound repair:

- Suppress hyperplastic, fibrotic tissue growth during post-injury remodeling phase;
- Enhance tissue removal during post-injury debridement phase.

Laser Osteotomy Using the Free Electron Laser: Effects of Energy Mode on Bone Healing, Remodeling, and Implant Stability

George M. Peavy, D.V.M., Bahman Anvari Ph.D., J. Stuart Nelson, M.D., Ph.D. .
University of California - Irvine, Beckman Laser Institute and Medical Clinic

John T. Payne, D.V.M., MS, and James L. Tomlinson, D.V.M., MVSc,
University of Missouri - Columbia, College of Veterinary Medicine

Lou Reinisch Ph.D.
Vanderbilt University - Medical FEL Center

Waifung Cheong, Ph.D.
Stanford University - FEL Center

Objective: To define the most appropriate wavelength and delivery mode for laser ablation of bone tissue.

Approach: Work currently in progress is investigating wavelengths at bone absorption peaks to define an appropriate wavelength for use in bone ablation procedures. Following the selection of an optimum wavelength, its application for bone ablation will be further refined by defining the most appropriate delivery mode (pulse sequence) for application, and evaluating the concurrent application of dynamic cooling to reduce any thermal injury at the ablation site.

Payoff: Defining a laser wavelength, delivery mode and application approach that will allow a laser system to be developed for orthopedic procedures.

Laser Osteotomy Using the Free Electron Laser: Effects of Energy Mode on Bone Healing, Remodeling, and Implant Stability

Animal Models:

Rat Tibia - investigation of 3 different delivery modes (pulse sequences)
Rabbit Tibia - investigation of concurrent application of dynamic cooling
Canine Ulna - in-vivo evaluation of defined wavelength, delivery mode and possible application of dynamic cooling.

Clinical Applications: Orthopedic procedures, including joint replacement and reconstructive surgery.

Equipment/Task	1996	1997				1998			
	4	1	2	3	4	1	2	3	4
Define Wavelength	X	X	X						
Beam Time	30 hrs								
Decision Points			◆						
Define Delivery Mode (pulse sequence)				X	X				
Beam Time VU-MFELC				30 hrs					
SU-FELC				16 hrs					
Decision Points					◆				
Evaluate Dynamic Cooling			X		X	X			
Beam Time					30 hrs				
Decision Points			◆			◆			
In-Vivo Application					X	X	X	X	X
Beam Time						30 hrs			
Decision Points									◆

Laser Applications For Wound Sterilization

George M. Peavy, D.V.M., and Bruce Tromberg, Ph.D.
University of California - Irvine, Beckman Laser Institute and Medical Clinic

Benjamin F. Edwards, Ph.D., James Carlson, Ph.D., Larry Galuppo, D.V.M., Bruce R. Madewell, D.V.M.
University of California - Davis, School of Veterinary Medicine

Eric Pope, D.V.M., MS, John N. Berg, D.V.M., Ph.D., Margaret A. Miller, D.V.M., Ph.D.
University of Missouri - Columbia, College of Veterinary Medicine

Kenneth E. Bartels, D.V.M., MS, Ernest L. Stair Jr., D.V.M., MS, Ph.D.,
Rebecca J. Morton, D.V.M., MS, Ph.D., Steven A Schafer, Ph.D., D. Thomas Dickey, D.V.M.
University of Oklahoma, College of Veterinary Medicine

Lou Reinisch Ph.D.
Vanderbilt University - Medical FEL Center

Objective: To evaluate the use of endogenous photochemical inactivation, selective photon absorption and chromophore enhanced photothermolysis as potential methods of sepsis control.

Approach: 1. Determine *in vitro* and then *in vivo* if endogenous photochemical compounds can be used for selective bactericidal activity.

2. Determine *in vitro* if specific bacteria have photon absorption peaks in the visual and infrared regions that are different than those for skin, muscle and blood. Determine *in vitro* if selective uptake of specific minerals can be used to enhance selective targeting of bacteria. Determine *in vivo* if specific wavelengths or the selective uptake of specific minerals by bacteria can be used to enhance selective targeting of bacteria for photothermolysis.

3. Determine *in vitro* if indocyanine green, indigo carmine, and carbon black can be used with commercially available solid state and diode laser systems to selectively kill bacteria. Determine *in vivo* if a dye chromophore and specific wavelength of laser light can be use for the selective thermolysis of bacteria without undue collateral soft tissue injury.

Payoff: Development of new methods for inactivating infectious agents.

Laser Applications For Wound Sterilization

Animal Models:

Mouse Abrasion Model
Rabbit Infected Wound Model

Clinical Applications: Sepsis control (wounds, burns, environmental decontamination)

Equipment/Task	1997				1998			
	1	2	3	4	1	2	3	4
Endogenous Photochemical Inactivation	X	X	X	X	X	X	X	
Beam Time (none needed)								
Decision Points				🍎			🍎	
Selective Photon Absorption	X	X	X	X	X	X	X	X
Beam Time (not yet determined)								
Decision Points				🍎			🍎	🍎
Chromophore Enhanced Photothermolysis	X	X	X	X	X	X	X	
Beam Time (none needed)								
Decision Points				🍎			🍎	

Title:	**Application of Free Electron Laser (FEL) in Bone Surgery**
Institution:	**Duke University**
Investigators:	**Longen Chen, PI** **James R. Urbaniak, Co-PI** **Anthony V. Seaber, Co-PI**
Collaborators:	**To be named**
Project Objective:	**Evaluation of infrared FEL as a tool for bone cutting**
Project Approach:	**Explore efficiency of bone cutting as a function of wavelength and power density** **Evaluate bone healing rate and quality compared with other bone cutting methods**
Project Payoff:	**Faster, stronger bone repair after FEL bone incision than with saw**

DukeFEL

Project title: Application of Free Electron Laser (FEL) in Bone Surgery

Institution: Duke University

Animal Model: Rat

Clinical Application: Bone incision for repair after trauma.
Replace other bone incision devices, because healing is faster and union is stronger.
Remove cement used with prior prostheses.

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Optimal laser parameters	→	→							
Healing Studies		→							
Beam time	4 hrs/wk	►	6 hrs/wk.						

↑ **Review bases for continued research**

Project title:	**Application of Free Electron Laser in Peripheral Nerve Surgery**
Institution:	**Duke University**
Investigators:	**Dr. Longen Chen, PI** **Dr. James R. Urbaniak, Co-PI** **Mr. Anthony V. Seaber, Co-PI**
Collaborators:	**To be named**
Project Objective:	**Test whether or not the FEL can make acceptable sections of peripheral nerve**
Project Approach:	**Section rat sciatic nerves - reapproximate them and do functional and histological studies of the reapproximated nerve**
Payoff:	**A much better method of sectioning the peripheral nerve in reparative/reconstructive surgery than now available**

Project title: Application of Free Electron Laser in Peripheral Nerve Surgery

Institution: Duke University

Animal Model: Rat

Clinical Application: Peripheral nerve repair - trauma and reconstructive procedures

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Optimal cutting parameters	→								
Functional recovery		→							
Analysis		→				→			
beam time:	4 hrs/wk. →					6 hrs/wk. →			

Project title:	**Parietal Cortex Lesions in the Rat**
Institution:	**Duke University**
Investigators:	**Blaine Nashold, Jr., PI** **Janice Ovelmen-Levitt, Co-PI** **Robert Pealstein, Co-PI** **Huaxin Sheng, Co-PI**
Collaborators:	**Michael Copeland, Vanderbilt**
Project Objective:	**Evaluate IR FEL as a surgical tool in the CNS**
Project Approach:	**Study, in the brain, FEL-induced lesion depth, collateral damage in both acute (4 hrs) and chronic (3 weeks) stages as a function of power density wavelength and number of laser pulses.**
Payoff:	**Lesions in the CNS which can be made with precision and with minimal collateral damage. Better than any method available today.**

Project title: **Parietal Cortex Lesions in the Rat**

Institution: **Duke University**

Clinical Application: **Production of Drez lesions in the spinal cord for pain control and removal of epileptic foci**

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4

Optimal parameters →

Electrophysiological studies ——→

Chronic studies ——→

↑ **Review bases for continued research**

Information exchange with Vanderbilt ——→

Project title:	**Free Electron Laser-Human Tissue (Skin) Interactions**
Institution:	**Duke University**
Investigators:	**Dr. Robert E. Clark, PI** **Dr. Shabnam Madani, Co PI**
Collaborators:	**Dr. Tom Flotte (MGH)**
Project Objective:	**Evaluate the FEL as a low-damage method for skin incision**
Project Approach:	**Using surviving human skin, establish optimal FEL parameters for low-damage skin incisions, assess the biological response of human skin to FEL incisions, and use miniature pigs to measure wound healing rates after FEL incisions**
Payoff:	**Low damage skin incisions - low inflammatory response**

Project title: Free Electron Laser-Human Tissue

Institution: Duke University

Animal Model: Miniature swine

Clinical application: Skin incision with low damage-precise removal of skin grafts with low damage

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Optimal parameters for linear cutting	→								
tissue staining standardization		→							
Immunohistology studies (human)			→						
Electron microscopy		→							
Miniature swine healing					→				
beam time → **4 hrs/wk.**		→							

Project title:	FEL Incision in Corneal Surgery
Institution:	Duke University
Investigators:	W. C. Fowler, PI John Rose, Co PI Alan D. Proia, Co PI
Collaborators:	Karen Joos (Vanderbilt)
Project Objective:	Evaluate the FEL operating in the ultra-violet as a tool for making corneal incisions
Project approach:	Cutting efficiency and collateral damage as a function of UV wavelength and power density will be measured in surviving pig cornea. This will be followed by long term corneal healing and stability of corrected cornea in rabbits. The final aspect of the study will utilize human blind eyes for refractive correction and healing rates.
Payoff:	Optimal ultraviolet wavelength and power density for corrective corneal surgery will be established.

Project title: FEL Incision in Corneal Surgery

Institution: Duke University

Animal Model: Surviving cornea from pig
New Zealand Rabbits

Human Studies: Final phase - 10 humans using blind eye

Clinical Application: Optimal corneal corrective surgery

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4

Optimal UV FEL Parameters ——————————→

Healing studies in Rabbits ——————————→

Human blind eye studies ——————→

Beam time ____ 6 hrs/wk ——→ 10 hrs/wk ——→ 6 hrs/wk ——→

Project title:	**Three-Dimensional Energy Selective Micro-Computed Tomography**
Institution:	**Duke University**
Investigators:	**G. Allan Johnson**
Collaborators:	**Carey Floyd, Duke** **Larry Hedlund, Duke**
Project Objective:	**Development of a three-dimensional volumetric computed tomographic system for <u>in vivo</u> microscipy of biologic specimens.**
Project approach:	**A 1800 x 2300 element detector (experimental from GE) will be interfaced to a high-speed data aquisition system and configured to accomodate real-time projection x-ray microscopy. Energy and time selective computed tomography. Energy and time selective subtraction microradiography will then be added. Finally, cone beam projection reconstruction algorithm will be used for 3 D computed tomography and 3 D energy selective computed tomography.**
Payoff:	**Sequential <u>in vivo</u> 3 D tomography whole small animals such as rats with microscopic resolution will make possible use of the same animal for sequential microscopic studies. This will save large numbers of animals and valuable time.**

Project title: Three-Dimensional Energy Selective Micro-Computed Tomography

Institution: Duke University

Animal Model: Rat

Clinical Application: Animal testing of pharmacological agents, trauma models etc, will be faster, cheaper, use fewer animals

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Delivery of detector		→							
Construction of synchrotron X-ray beam line		→	→	→					
Real time X-ray projection microscopy				→	→	→	→		
Subtraction micro-radiography				→	→	→	→		
Algorithm development			→	→	→				
Beam time		8 hrs/wk	→	→	→	→	→	→	→

Project title:	**Free Electron Laser Interaction with Ocular Tissues: A Surgical Benefit?**
Institution:	**Duke University**
Investigators:	**Cynthia A Toth**
Collaborators:	**K. Joos (Vanderbilt), D. Jansen, M. Frenz, A. J. Welch (U. of Tex, Austin), B. Rockwell, (Armstrong Laboratories) D. Katz (Duke), J. S. Nelson (Beckman)**
Project Objective:	**Identify optimal ablation wavelength in the infrared which will induce minimal collateral damage and minimal tissue healing response in the posterior segment of the eye.**
Project approach:	**Model collagen patches placed in vitreous of enucleated pig eyes will be used for wavelength and power density studies. This will be followed by whole animal studies (rabbit) to assess tissue response and compare with standard surgical and Er:YAG laser surgical incision in eyes which have induced scars. Fiber optic delivery will be required and perflubron perfusion to limit unwanted absorbtion will also be tested.**
Payoff:	**Demonstration of low - damage removal of posterior segment scars. Use of perflubron to deliver power in tissue.**

Project title: **Free Electron Laser Interaction with Ocular Tissues: A Surgical Benefit?**

Institution: **Duke University**

Animal Model: **Enucleated pig eyes**
Rabbit

Clinical Application: **Removal of pre-retinal scar and low damage posterior segment surgery of the eye**

Milestones

	1996	1997				1998
Quarter:	4	1	2	3	4	1
Enucleated pig	→	→	→	→	→	
Retinal motion sensor testing	→	→	→	→		
Testing of fiber optics at 2.94 μ	→	→	→	→		
Testing of OCT		→	→	→	→	
Rabbit acute and chronic studies		→	→	→	→	→
Perflubron perfusion studies				→	→	→
beam time	4 hrs/wk →	8 hrs/wk →	→	→	→	→

Project title: **Exploration of Coherent Dark-Field Detection As a Means to Detect CBW Agents and Pathogens**

Institution: **Duke University**

Animal Model: **N/A**

Clinical Application: **Early warning - sensitive, reliable detection of CBW agents**

Milestones

	1996	1997				1998			
Quarter:	4	1	2	3	4	1	2	3	4
Detection of Dark-Field signatures of model compounds	→	→	→	→	→				
Exploration of Dark-Field signatures of non-pathogenic bacteria		→	→	→	→	→	→	→	→
Exploration of scattering		→	→	→	→	→	→	→	→
Indoor range experiments					→	→	→	→	→
Beam time 4 hrs/wk	→	→	→	→	→	→	→	→	→

Project title: **Exploration of Coherent Dark-Field Detection As a Means to Detect CBW Agents and Pathogens**

Institution: **Duke University**

Investigator: **John M. J. Madey**

Project Objective: **Detection of CBW agents and pathogens under battlefield conditions**

Project approach: **Utilize the coherent, dark field scattered return between pulses of the infrared FEL to increase sensitivity of detection of absorbing chromophores**

Payoff: **Increase sensitivity of presently available sensing devices by order (s) of magnitude**

Project title	**Infrared Transmitting Fiber Optics for Delivery of Laser Radiation in the 2 to 9 μm Spectral Region**
Institution	**Duke/FDA**
Investigator	**R. W. Waynant**
Project Objective	**Development of fiber optics with lenses suitable for use in the mid-IR region**
Project approach	**Solid and hollow waveguides with suitable lenses will be tested for use with high peak pulsed power in the < 3.4 μ region. Concentric fiber optic-outside catheter systems will be tested for delivery of perflubron and deuterium oxide solutions to the field of irradiation.**
Payoff	**Delivery of high peak pulsed FEL power to surgical field through surgically useful fiber optic system.**

Project title **Infrared Transmitting Fiber Optics for Delivery of Laser Radiation in the 2 to 9 μm Spectral Region**

Institution **Duke University**

Animal Model **As per other investigators**

Clinical Application **Delivery of FEL power through suitably flexible fiber optics allows surgery in areas such as eyes which are not accessible with open beam optics.**

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Hollow waveguide at 2.94 μ	→								
Solid waveguide at 2.94 μ	→								
Lenses for 2.94 μ	→	→	→	→					
Hollow waveguide for 6.45 μ	→	→	→	→	→	→	→	→	
Concentric delivery system	→	→	→	→	→	→	→	→	
Beam time 6 hrs/wk	→	→	→	→	→	→	→	→	

Project title: **Biological X-Ray Analysis Using A FEL**

Institution: **Duke University**

Investigator: **E. A. Le Furgey, Co PI**
P. Ingram, Co PI

Project Objective:

(A.) Design, contruct and test x-ray fluoresence microscope using high brightness x-ray from mm wave FEL inverse Compton source

(B.) Improve on microprobe techniques currently available

(C.) Improve elemental sensitivity and spacial resolution of microprobe techniques

Project approach: **Using a special stage and x-ray optics, construct a a scanning electron microscope which can collect structural data (electron imaging) and elemental distribution data (x-ray microprobe) on the same sample.**

Payoff: **Demonstration of order of magnitude increases in sensitivity of microprobe elemental analysis on cellular and subcellular levels.**

Project title	**Biological X-Ray Analysis Using A FEL**
Institution	**Duke University**
Animal Model:	**Rat; invertebrates**
Clinical Application	**Localization of toxic elements in cells-tracing toxic or indicator elements in food chain - CBW response in man**

Milestones

	1996	1997				1998			
Quarter	4	1	2	3	4	1	2	3	4
Fabrication of stage	→								
Construction of synchrotron x-ray beamline	→								
X-ray optic development	→								
X-ray microprobe using synchrotron sources			→						
Review bases for continued research		↑							
Beam time		**12 hrs/wk**	→						

Project title: **Soft X-Ray Imaging of Living Cells**

Institution: **Duke University**

Investigator: **J. M. J. Madey, PI**
L. Johnson, G. Denbeaux

Project Objective: **To produce high resolution images of living cells**

Project approach: **Using quasicoherent 4 Å radiation from an undulator on the 1 GeV Duke Storage Ring, utilize the contrast between oxygen and carbon to make images of living cells by contact micrography on a photoresist and/or projection imaging on a high resolution CCD array.**

Payoff: **100 Å resolution images of living cells**

DukeFEL

Project title	**Soft X-Ray Microscopy of Living Cells**
Institution	**Duke University**
Animal Model	**Invertebrates**
Clinical Application	**Soft X-ray microscopy will allow for the first time the overall structure of living cells (water still present) to be seen at high resolution. Disruption of water dependent cellular structures is a basic pathological response of all cells and protection from acute cellular damage will be greatly aided by information developed by this technique.**

Milestones

	1996	1997				1998			
Quarter	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
NIST undulator on beamline	→	→	→	→					
Beamline construction	→	→	→	→					
Wavelength and power measurements	→	→	→	→					
Exploration of contact micrography				→	→	→	→	→	
Exploration of projection micrography				→	→	→	→	→	
Beam time 8 hrs/wk	→	→	→	→	→	→	→	→	

Duke FEL

Project title	**Studies on Multiphoton Dissociation of Small Molecules In the Gas Phase**
Institution	**Duke University**
Investigator	**K. D. Straub**
Collaborators	**A. Petrov, J. Chesnikov, Y. Molin (ICKC, Novosibirsk)**
Project Objective	**Explore the multiphoton reactions in small molecules in the gas phase in the mid-IR. Develop photosensitized destruction of toxic molecules by MPD.**
Project approach	**Optimal parameters for MPD of small molecules including coherence, wavelength, power and optical "chirp" in molecules such as formic acid, water, etc., are explored using mass spectrum analysis.**
Payoff	**Demonstration of effectiveness of FEL radiation for multi-photon chemistry at high pressure**

Single Micropulse Ablation/Stanford University

Point of Contact: H. Alan Schwettman, Michael D. Fayer

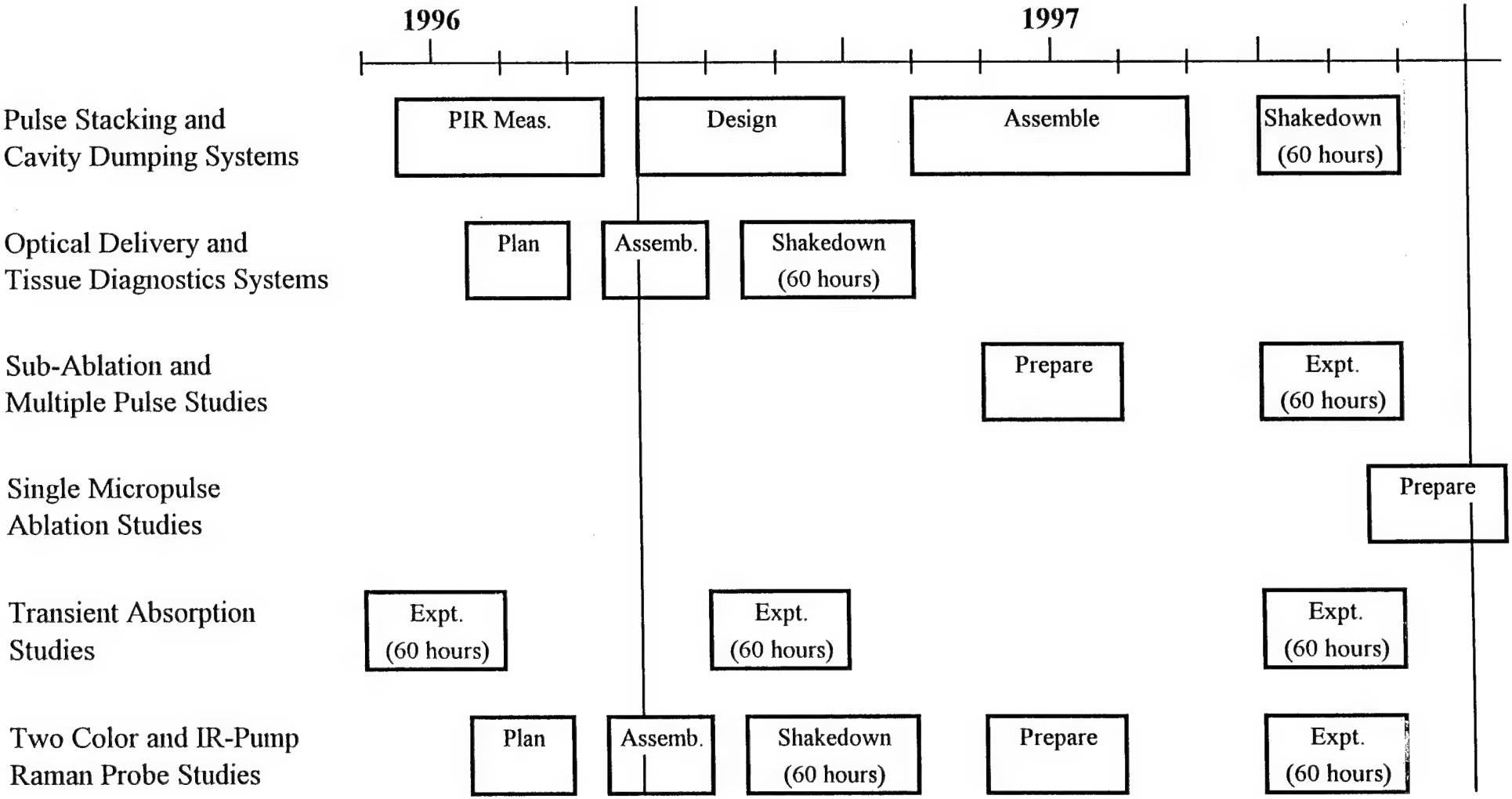
Collaborators: Norman Nishioka, M.D., Wellman Laboratories, M.G.H.
Kristen A. Peterson, New Mexico State University

Project Objectives: Characterize tissue ablation for ultra short infrared optical pulses.

Project Approach: By pulse stacking and focusing the FEL beam, the ablation threshold for tissue can be exceeded by a significant margin in a single micropulse. Optical transmission measurements, real-time thermal-mechanical measurements and histological analysis will be used to characterize the ablation process. Vibrational dynamics techniques (transient absorption, two color pump-probe, and IR pump/Raman probe) will be used to study the energy redistribution process.

Payoff: Guidance in selecting laser parameters for surgery applications.

Single Micropulse Ablation/Stanford University
Milestone Chart



Scanning Near Field Infrared Microscopy/Stanford University

Point of Contact: Todd I. Smith

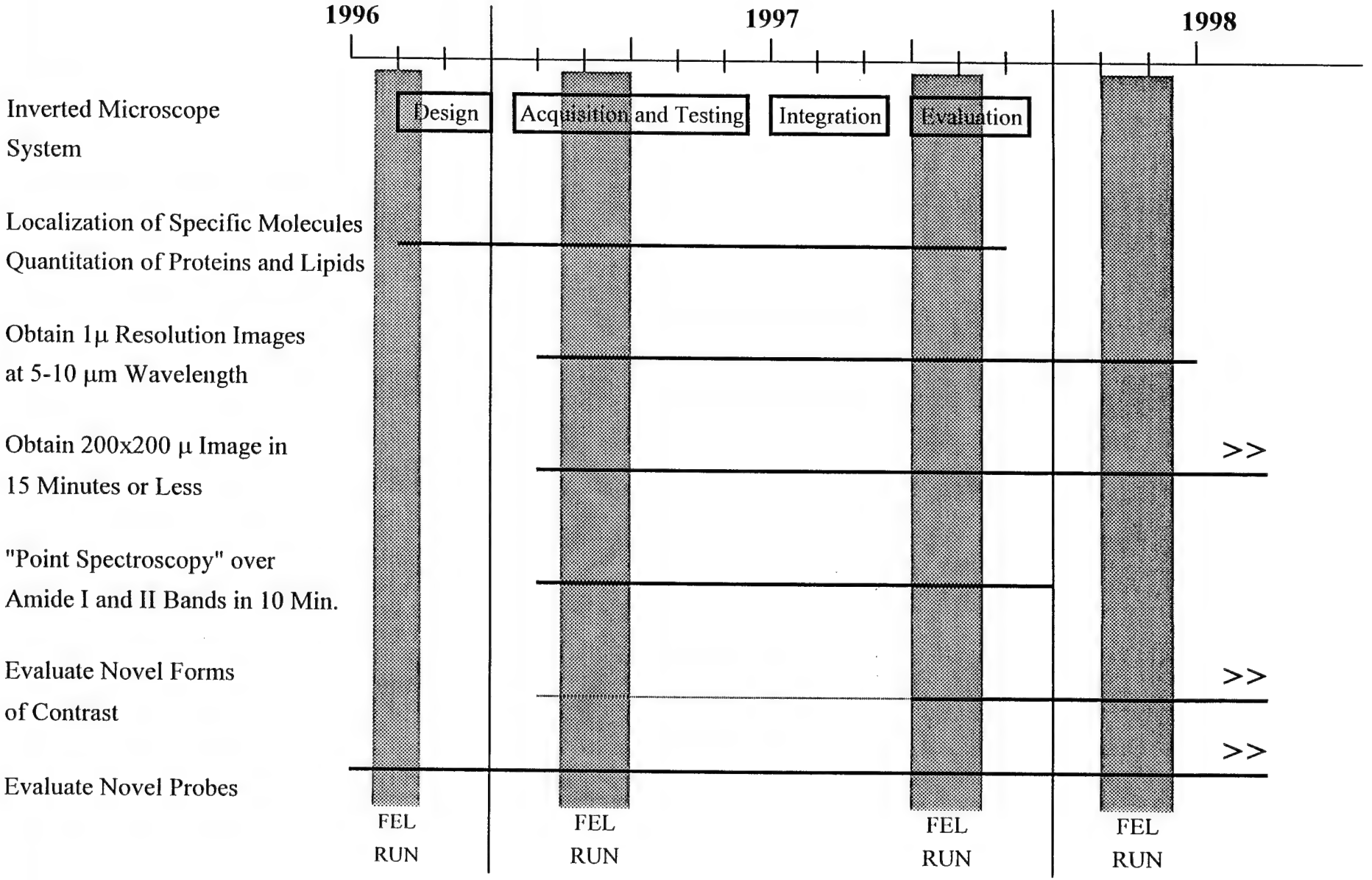
Collaborators: Shyamsunder Erramilli, Mi K. Hong; Boston University

Project Objectives: Develop scanning near field microscopy as an imaging tool for bio-medical applications.

Project Approach: A prototype scanning near field infrared microscope using infrared transmitting fibers has been developed in a collaboration between Stanford and Boston Universities. An improved version of the microscope will be constructed and used to demonstrate high resolution spectroscopic imaging of biological samples.

Payoff: A new imaging technique may help understand a variety of medical conditions.

Scanning Near Field Infrared Microscopy/Stanford University
Milestone Chart



Soft Tissue Surgery

Project Title:	FEL Applications for Neurosurgery/Tissue Interactions and Wound Healing in the Upper Respiratory Tract/FEL Welding Procedure Development and Wound Healing in Ocular Tissues/Molecular Biophysics
Institution:	Vanderbilt University
P.I.'s:	Michael Copeland/Gaelyn Garrett/Karen Joos/Glenn Edwards
Collaborators:	Vivien Casagrande, Jeff Davidson, and James McKanna. Rox Anderson, Tom Flotte, and Cynthia Toth.
Project Objective:	Conduct animal studies necessary to justify FEL applications to human surgery. Elucidate mechanisms governing ablation.
Project Approach:	Animal models have been identified for each medical specialty to pursue clinical and surgical applications of FEL tissue ablation and FEL tissue welding. Surgical procedures have been identified for initial applications. Beam delivery issues are being addressed by collaborating physicists and biomedical engineers. Wound healing issues are being addressed by collaborating biomedical scientists.
Payoff:	Potential for improved medical care based on novel FEL-based protocols.

Project Title: FEL Applications for Neurosurgery/Tissue Interactions and Wound Healing in the Upper Respiratory Tract/FEL Welding Procedure Development and Wound Healing in Ocular Tissues

Institution: Vanderbilt University

Animal Models:

FEL Applications for Neurosurgery
canine, pig

Tissue Interactions and Wound Healing in the Upper Respiratory Tract
canine

FEL Welding Procedure Development and Wound Healing in Ocular Tissues
rabbits, monkeys, and pigs

Clinical Applications:

FEL Applications for Neurosurgery
corticotomy
brain debridement
mass lesion resection
quantitative measurement of brain injury

Tissue Interactions and Wound Healing in the Upper Respiratory Tract
surgical treatment of subglottic stenosis (SGS)
surgical treatment of posterior glottic scar (PGS)
minimize hypertrophic scar formation

FEL Welding Procedure Development and Wound Healing in Ocular Tissues
retinal welding
repair of ocular lacerations

Milestones

	1997				1998				1999	
	1	2	3	4	1	2	3	4	1	2
Neurosurgery	data analysis			IRB application		Human application				
	endovascular (flow chamber)					endovascular (animal experiments)				
Otolaryngology	SGS/PGS----------									
Ophthalmology:										
laser parameter identification				X	X					
rabbit studies					X	X	X			
monkey studies									X	X

Hard Tissue Surgery

Project Title:	Selective Modification of Materials/Hard-Tissue Modification and Wound Healing Mechanisms/Molecular Biophysics
Institution:	Vanderbilt University
P.I.'s:	Norman Tolk/Richard Haglund/Glenn Edwards
Collaborators:	Jeff Davidson, Hee Park, Tom Milner
Project Objective:	Elucidate mechanisms, applications to dental surgery and biomaterials, cartilage reshaping
Project Approach:	Investigate mechanisms of hard-tissue ablation, hydroxyapatite deposition, and cartilage reshaping with the aim of developing clinical applications.
Payoff:	Basic research with the potential for enabling biomedical research and clinical applications

Project Title: Selective Modification of Materials/Hard-Tissue Modification and Wound Healing Mechanisms/Molecular Biophysics

Institution: Vanderbilt University

Animal Models: TBN

Clinical Applications: Dental surgery, biocompatibility, and cartilage surgery

Milestones

	1997				1998				1999	
	1	2	3	4	1	2	3	4	1	2
Mechanisms	----------									
Dental ablation					----------					
Hydroxyapatite deposition								----------		
Cartilage Reshaping	----------									

Diagnostics/Imaging

Monochromatic X-ray Project

Vanderbilt University FEL Center

P.I. - Frank Carroll, M.D.

Key personnel:
James Waters, Ph.D.
Weiwei Clark, Ph.D.
Charles Brau, Ph.D.
Robert Traeger
Ron Price, Ph.D.
David Pickens, Ph.D.

Major collaborators:
James Nelson, M.D.
University of Washington Seattle
Todd Smith, Ph.D.
Stanford University
FDA/LLNL - TOF detectors

Objective: - Production and Use of Monochromatic X-rays for Diagnosis and Treatment in Medicine

Approach: - Compton Scatter, mosaic crystals, standard imaging,Time-of-flight and phase imaging

Payoff: - Earlier and more accurate diagnosis of breast cancer, as well as improved imaging in all facets of medicine. Improved therapy.

Monochromatic X-ray Project

Vanderbilt University FEL Center

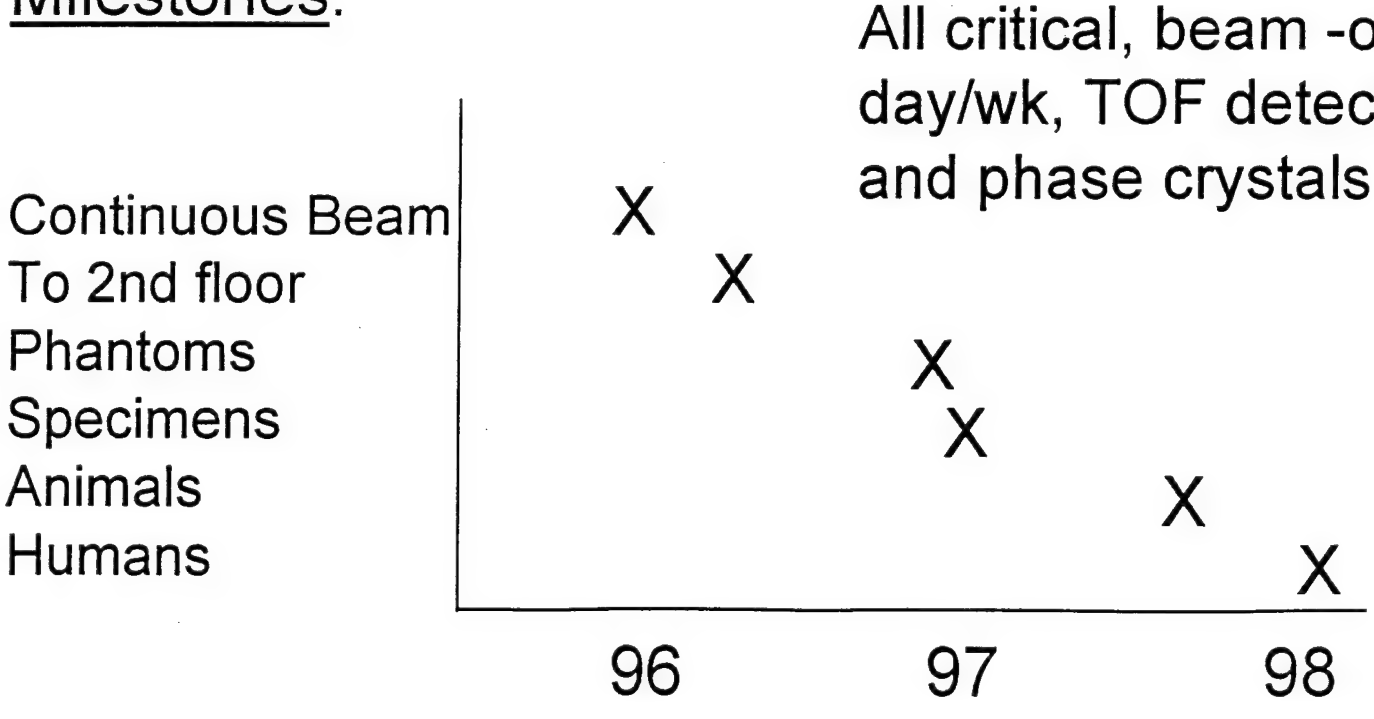
Models:

Tissue - Excised specimens up to whole breasts.
Animal - Mouse (rabbit) - tumor/ChemoradioRx
Dead animals - tissue injuries/trauma

Clinical Applications:

Breast cancer - Dx and Rx. Improved Sens./Spec.
Other X-ray applics. - marked improvement S/N

Milestones:



Tissue Welding

Project Title:	Molecular Biophysics/FEL Welding Procedure Development and Wound Healing in Ocular Tissues
Institution:	Vanderbilt University
P.I.'s:	Glenn Edwards/Karen Joos/Vivien Casagrande
Collaborators:	Jeff Davidson
Project Objective:	Pursue observation of FEL induced photo-association of protein as potential mechanism for tissue welding/develop clinical procedures in ophthalmology
Project Approach:	The mechanism for the photo-association will be established by biophysical investigations. Clinical procedures will be developed in ophthalmology. Physiological consequences will be monitored by cell biologists. Beam delivery issues are being addressed by collaborating physicists and biomedical engineers.
Payoff:	The potential demonstration of IR photoproducts. Non-contact tissue welding.

Project Title: Molecular Biophysics/FEL Welding Procedure Development and Wound Healing in Ocular Tissues

Institution: Vanderbilt University

Animal Models: FEL Welding Procedure Development and Wound Healing in Ocular Tissues
rabbits, monkeys, and pigs

Clinical Applications: retinal welding
repair of ocular lacerations

Milestones

	1997				1998				1999	
	1	2	3	4	1	2	3	4	1	2
mechanisms	X	X								
beam delivery	X	X	X	X						
laser parameter identification				X	X					
rabbit studies					X	X	X			
monkey studies									X	X
two-shifts per week										

Wound Healing-Cell Biology/Vanderbilt

Jeff Davidson, Ph.D. *Cutaneous Wound Repair*	Vivien Casagrande, Ph.D. *Ocular Tissue Welding*	Jim McKanna, Ph.D. *Wound Healing and Regeneration in Neural Tissues*
Lillian B. Nanney, Ph.D. Jeff Whitsitt, M.D.	Karen Joos, M.D., Ph.D. Jin Shen, Ph.D.	Michael Copeland, M.D., Ph.D.

Collaborators

Wound Debridement - Nishioka/Wellman Gene Therapy - Flotte/Wellman Skin Resurfacing - Anderson/Wellman Haglund/Vanderbilt Wound Healing - Reinisch/Vanderbilt Clark/Duke Macrophage PDT - Tromberg/Beckman Hasan/ Wellman	Ocular tissue welding - Edwards/VU Ocular histology -Shetlar/VU; Toth/Duke Glial/neural response - McKanna/VU Collagen remodeling - Davidson/VU	Phagocyte types/responses - Shepherd/VU Microglia:CNS damage -Joos,Copeland/VU Sciatic regeneration - Zealar/VU Microglia:Optic nerve regeneration -Joos, Casagrande/VU

Objectives

Ablation vs. wavelength, pulse rate, fluence Incision vs. wavelength, pulse rate, fluence Chemical burn debridement Collagen remodeling Gene therapy of wounds/skin Macrophage modulation	Retinal welding vs. laser parameters Scleral welding vs. laser parameters Corneal welding vs. laser parameters Glial responses vs. laser parameters Neuronal responses vs laser parameters Collagen remodeling	Glial responses vs. laser parameters CNS damage vs FEL and other surgeries Phagocytes in sciatic nerve regeneration Phagocytes in optic nerve damage Microglia in animal models of CNS surgery

Approach

Biochemical, histological, and biomechanical evaluation of wound sites Biochemical model of laser-collagen interactions: x-links, 2° structure FEL/conventional laser photoacoustics for DNA transfection of therapeutics PDT manipulation of macrophage function in wound models	FEL welding of detached retina Quantitative image analysis FEL welding of non-retinal ocular lacerations Immunocytochemical evaluation of retinal/ocular damage FEL repair/welding parameters	FEL and other lesions to sciatic and optic nerves Immunohistochemical identification of microglia and macrophages Quantitative image analysis

Payoffs

Develop therapeutic FEL applications Validate, at a mechanistic level, the role of the FEL as a surgical and medical device	Therapeutic FEL applications to ocular surgery Novel tissue welding protocols using the FEL Objective evaluation of retinal/ocular damage Better understanding of neural tissue response to ocular damage and repair	Objective evaluation of CNS damage Identity and lineage of CNS phagocytes Evaluate ± influences of FEL parameters in CNS surgery Long term: promote CNS healing and regeneration

Wound Healing-Cell Biology/Vanderbilt

Cutaneous Wound Repair	*Ocular Tissue Welding*	*Wound Healing and Regeneration in Neural Tissues*
Jeffrey M. Davidson, Ph.D. Lillian B. Nanney, Ph.D. Jeff Whitsitt, M.D.	Vivien Casagrande, Ph.D. Karen Joos, M.D., Ph.D. Jin Shen, Ph.D.	Jim McKanna, Ph.D. Michael Copeland, M.D., Ph.D.

Animal Models

Tissue Ablation - Rabbit/Pig	Initial welding experiments: - cadaveric human/porcine eyes	Sciatic nerve - rat
Incisional Repair - Rat/Pig	Retinal detachment - rabbit/monkey	Optic nerve - rat, rabbit, monkey
Chemical Burn Debridement - Rat/Rabbit	Non-retinal ocular tissue - rabbit/monkey	Brain incisions and ablation - rat,dog
Macrophage PDT - Rat		

Clinical Applications

Plastic Surgery	Ocular surgery	Neurology and neurosurgery
Dermatologic Surgery	Plastic surgery	Ophthalmology
Burn care	Future - modulation of glial/neural responses	
Chronic wounds		
Skin resurfacing		
Inflammatory disease		

Milestones

Quarter	1/97	2/97	3/97	4/97	1/98	2/98	3/98	4/98	1/99	2/99
Task										
Ablation	→	→	→	→						
Incision	→	→	→	→	→	→	→	→	→	
Collagen denaturation			→	→	→	→	→	→		
Gene Therapy and Wound Healing			→	→	→	→	→	→	→	→
Macrophage PDT				→	→	→	→	→	→	→
CNS phagocyte types	→	→	→	→	→	→	→			
Sciatic nerve		→	→	→	→	→				
Optic nerve			→	→	→	→	→			
Glial responses in incision and ablation		→	→	→	→	→	→	→	→	→
Retinal detachment	→	→	→	→	→	→	→	→	→	→
Cellular responses vs. laser parameters			→	→	→	→	→	→	→	→
Scleral welding			→	→	→	→	→	→	→	→
Corneal welding	→	→	→	→	→	→	→			
Collagen remodeling			→	→	→	→	→	→	→	→
Equipment										
Beam Time, shifts/week	3	3	3	4	4	4	4	4	4	4

Core Operations/Vanderbilt University

Contacts : Bill Gabella also Marcus Mendenhall, Rick Grant, John Kozub, Ed Mone, Scott Storms

Objective : Increase quality of hours delivered to users, improve machine diagnostics, understand and make more reliable FEL tuning

Approach : Add diagnostics where feasible, study FEL tuning

Payoff : Better scientific results, quicker better tuning

Reliability Improvements/Vanderbilt University

Contacts : Bill Gabella and Operations Group

Collaborators : Bob Traeger (X-Ray Group), Bob Gardenghi, Myron Wheeler

Objective : Improve FEL reliability, especially the pulsed power system, study/increase FEL laser power

Approach : Hired consultants from industry, implementing a plan of "basics" (modulator air cooling, clean transformer oil, etc)

Payoff : Less downtime due to improved components, enhanced performance, more time for other operational issues

Beam Delivery/Vanderbilt University

Contacts : Marcus Mendenhall, Glenn Edwards, Terry King, Jin Hui Shen

Objective : Deliver beam to the human operating rooms, to the bullpen labs, and into patients and subjects; delivery devices for surgical application

Approach : Nearly straightforward extension of current IR transport system; non-articulated arm delivery systems

Payoff : Human patient procedures, more power into/onto the subject

Research to Develop Biomedical Applications of Free Electron Laser Technology

Revised Work Statement for 1997-98

John A. Parrish, M.D.
Principal Investigator, Wellman Laboratories of Photomedicine

The proposed work and budget for the Wellman Laboratories have been revised in accordance with the recommendations of the review panel. We are committed to accelerating the efforts to realize near-term medical payoffs and expanding our collaborations with the other MFEL Centers. We view our efforts as an integrated program of basic and applied research with the belief that an understanding of the mechanisms of laser-tissue interactions will permit better development of diagnostic and therapeutic applications. In order to facilitate the development of FEL applications and to foster our interactions with the FEL centers, we are planning to fund investigators at the FEL centers.

The revised plan will include the following sections from the original proposal:

A. Wound Healing
   1. Photoimmunotherapy for the local control of sepsis
   2. Treatment and diagnosis of chemical burn injury
   3. Macrophage targeted PDT regulation of wound healing
   4. Stress wave enhanced gene therapy for wound healing

B. Light-activated tissue repair

C. Spatially confined pulsed laser effects
   1. MIcroparticle targetting
   2. FEL-generated evanescent wave interactions and Development of evanescent-wave FEL scalpel
   3. Pulsed laser reversal of cerebral artery vasospasm

D. Effects of UVFEL radiation on biological molecules

E. Tissue effects of laser-induced stress waves
   1. In vivo applications
   2. Unipolar laser-induced tensile waves
   3. Influence of temporal pulse structure and wavelength on the response of tissue to mid-IR FEL laser irradiation.

Wellman laboratories of Photomedicine

Project Title:	Photoimmunotherapy for the Local Control of Sepsis
Principal Investigator:	Tayyaba Hasan, Ph.D.
Key Personnel:	Michael Hamblin, Ph.D. Jaimie Miller, B.S.
Collaborators:	Jeffrey Davidson, Vanderbilt David Benaron, Stanford
Project Objective:	To establish the role of local sepsis control in wound healing by bacteria using antibody/peptide targeted sensitizers
Project Approach:	Photosensitizer conjugate syntheses and testing *in vitro* to establish efficacy parameters. These will then be tested in an infected wound model *in vivo*.
Payoff:	This study is expected to provide a means of rapid sterilization of infected wounds so as to lead to accelerated wound healing

Project Title:	Photoimmunotherapy for the Local Control of Sepsis
Animal Model:	Mouse skin incisional model
Tasks:	1. Synthesize and characterize conjugates 2. In vitro uptake by bacteria and mammalian cells 3. In vitro photoinactivation of P. aerug. 4. In vitro photoinactivation of E. coli 5. Optimize photoinactivation parameters in vitro 6. In vivo mouse model - local administration 7. In vivo mouse model - systemic administration 8. Optimize photoinactivation parameters in vivo

Milestone Chart:

1997

Task	1	2	3	4
1	X	X		
2	X	X	X	
3		X	X	X
4			X	X

1998

Task	1	2	3	4
5	X	X		
6	X	X	X	X
7			X	X
8			X	X

Wellman laboratories of Photomedicine

Project Title:	Macrophage Targeted Photodynamic Regulation of Wound Healing
Principal Investigator:	Tayyaba Hasan, Ph.D.
Key Personnel:	Michael Hamblin, Ph.D. Norah Chen, B.S. Nedret Altiok, M.D., Ph.D.
Collaborators:	Bruce Tromberg, Backman Jeffery Davidson, Vanderbilt
Project Objective:	Demonstrate the photosensitized regulation of macrophage function for the acceleration of wound healing and the inhibition of adhesion formation.
Project Approach:	Targeting of photosensitizer conjugates to different macrophage receptors so as to elicit appropriate macrophage function modulation.
Payoff:	Wounds in the aged population or diabetics are often slow to heal. Battlefield injuries may also have wounds that are slow to heal due to infection or stress. Accelerated wound healing would be beneficial in both of these contexts. Normal surgical procedures or battlefield injuries may lead to adhesions which is often a cause of delayed recovery. These studies are aimed at reducing adhesion formation due to trauma.

Project Title:	Macrophage Targeted Photodynamic Regulation of Wound Healing
Animal Model:	Rat incisional model Rabbit ear model Rat intra-abdominal adhesion model
Tasks:	1. Synthesize and characterize targeting moeities 2. Uptake and imaging in cells 3. In vitro photosensitization cytokine release and cytotoxicity from macrophages 4. Photosensitized cytokine release and cytotoxicity of companion cells 5. Photosensitized growth and migration of companion cells 6. Photosensitized modulation of wound healing in the rat incisional model 7. Photosensitized modulation of abdominal adhesion model 8. Photosensitized modulation in rabbit ear ulcer model

Wellman laboratories of Photomedicine

Project Title:	Stress wave enhanced gene therapy for wound healing
Principal Investigator:	Thomas J. Flotte, M.D.
Key Personnel:	Apostolos Doukas, Ph.D. Shun Lee, Ph.D.
Collaborators	Jeffrey M. Davidson, Vanderbilt
Project Objective:	To demonstrate that laser-induced stress-wave assisted gene therapy can accelerate wound healing
Project Approach:	The approach will be use to laser-induced stress-waves to deliver appropriate genes to create transient expression of TGF-ß1 in full thickness skin incisions as a means of enhancing the rate of wound repair.
Payoff:	A new method for molecular delivery that may be used for a variety of applications such as decreased time for recovery from wounds. Development of new approach for drug delivery which may result in new classes of drugs.

Project Title:	Stress wave enhanced gene therapy for wound healing
Animal Models:	Sprague-Dawley rat model of healing of skin incisions
Clinical applications:	Improved healing of acute wounds and non-healing ulcers
Milestones	Demonstration molecular delivery into the skin Demonstration of expression of gene products Demonstration of increased healing

Wellman Laboratories of Photomedicine

Project Title:	Influence of Temporal Pulse Structure and Wavelength on the Response of Tissue to Mid-IR FEL Irradiation
Principal Investigator:	Norm Nishioka, M.D.
Collaborator:	Alan Schwettman, Stanford
Project Objective:	Determine the relative influence of wavelength and pulse structure on tissue mechanical response and ablation dynamics Assess the diagnostic utility of tissue mechanical response
Project Approach:	Simultaneously measure the stress, displacement and temperature response of tissue to both ablative and subablative laser pulses for various wavelengths and pulse durations Detailed microscopic assessment of ablation craters using light and electron microscopy Develop theoretical models of tissue response Explore whether tissue mechanical responses to sub-ablative doses of laser irradiation provide useful diagnostic information about the tissue
Payoff:	Bloodless, efficient laser debridement and grafting with optimized rate of healing Decontaminate chemical/biological skin surface warfare agents Evaluate healing outcome for burns of indiscriminate depths

Project Title:	Influence of Temporal Pulse Structure and Wavelength on the Response of Tissue to Mid-IR FEL Irradiation
Beam Time:	~40 hours 2.95, 4.7, 5.99, 6.45, 6.75, 8.2, 10.6 μm 1-30 μJ, micropulses (singly, stacked or in sequence) Spot size: ~100 μm

Wellman laboratories of Photomedicine

Project Title:	FEL-Generated Refracted and Evanescent Waves for Surgery
Principal Investigator:	R. Rox Anderson, M.D.
Key Personnel:	Charles Lin, Ph.D. Ycov Domankevitez Brett Hooper, Ph.D.
Project Objective:	Understand, design, and implement a new class of contact laser surgery devices
Project Approach:	Determine the practical range of control over depth of optical penetration and tissue interaction, which can be obtained by varying refraction angle Characterize primary damage to soft tissues for e-wave and refracted FEL macropulses at wavelengths absorbed primarily by water Ablate tissue with FEL-generated evanescent waves at the margin of optical waveguides Build and test prototype FEL-pumped tissue ablation tools a. Contact surgery with e-wave and refracted beam b. Precise intra-luminal ablation tool
Payoff:	A new class of contact, pulsed laser surgical tools should come from this project, including better control over FEL tissue ablation.

Project Title:	FEL-Generated Refracted and Evanescent Waves for Surgery
Animal Models:	Porcine artery, skin and cornea
Milestones/ decision points	Demonstration of ablation efficiency sufficient for surgical practicality Demonstration of rough tissue surface smoothing Demonstration of silica devices for e-wave and refraction Demonstration of ablation at a waveguide-tissue interface Fabrication of prototype surgical device
FEL Beam time	1-2 days/week Macropulse energy at 2.7 μm (ideally, of at least 10 mJ)

Wellman laboratories of Photomedicine

Project Title:	Treatment and Diagnosis of Chemical Burn Injury
Principal Investigator:	Norm Nishioka, M.D.
Collaborator:	Jeff Davidson, Vanderbilt
Project Objective:	Compare the FEL and CO_2 laser pulses for debriding chemical burns Assess the accuracy of ICG fluorescence for evaluating the depth of chemical burns
Project Approach:	Create chemical burns in porcine skin using intradermal injections of Adriamycin Evaluate depth of burns with ICG fluorescence Debride using 6.45 μm FEL and 10.6 μm CO_2 Evaluate graft-take and rate of healing
Payoff:	Bloodless, efficient laser debridement and grafting with optimized rate of healing Decontaminate chemical/biological skin surface warfare agents Evaluate healing outcome for burns of indiscriminate depths

Project Title:	Treatment and Diagnosis of Chemical Burn Injury
Animal Models:	Adriamycin burns in porcine skin
Clinical Applications:	None planned
Milestone Chart:	Work in progress
Beam Time:	OR time: ~18 hours, Beam Time: ~6 hours 6.45 μm FEL for debriding burns Max. energy, Max. Rep. Rate Spot size: TBD

Wellman laboratories of Photomedicine

Project Title:	Light-activated tissue repair
Principal Investigator:	R. Rox Anderson, M.D. Irene E. Kochavar, Ph.D.
Key Personnel:	David Lin, Ph.D. Bobby Redmond, Ph.D.
Project Objective:	Develop dye-mediated enhancement of pulsed laser photothermal tissue repair and compare to conventional suture repairs in skin and tendon. Develop a series of molecular crosslinking systems for type I collagen and test in vitro repair of connective tissues.
Project Approach:	Use of a tissue-binding dye, to provide (a) selective absorption of deeply penetrating laser light for local heating, (b) a local monitor of temperature and/or collagen unwinding used to control laser pulse energy, and (c) the option of photosensitized crosslinking of the weld enhanced strength. Design and synthesize bifunctional collagen cross-linking at fiber cleavage site. Investigate and optimize the efficacy of photochemical crosslinking via singlet oxygen, electron transfer, and free radical mechanisms.
Payoff:	Light-activated tissue repair provides hemostasis, precision, speed, strength, ability to seal against fluid leaks, compatibility with endoscopic surgery, and lack of foreign body response. Civilian and military personnel suffering from trauma or wounds may benefit from this alternative to conventional suture repairs.

Project Title:	Light-activated tissue repair
Animal Model:	Pig skin and rabbit achilles tendon models
Clinical Appl.	Rapid, sutureless repair of connective tissue.
Tasks:	1. Study dye fluorescence as a local monitor of temperature and/or collagen unwinding used to control laser pulse energy 2. Investigate singlet oxygen and electron transfer mechanisms for collagen crosslinking 3. Determine the efficacy of photochemically generated free radicals for inducing crosslinks. 4. Design and synthesize bifunctional collagen-targeted photoactivators for specific localizaton of collagen crosslinking at fiber cleavage site. 5. In vivo testing of photothermal welding using pig skin and rabbit achilles tendon as model connective tissues.